Exhibit 1

The Causal Relationship Between Prenatal Acetaminophen Use, Neurodevelopmental Disorders (NDD), Attention-Deficit/Hyperactivity Disorder (ADHD), and Autism Spectrum Disorder (ASD).

Expert Report of Andrea Baccarelli, MD, PhD, MPH

A. EXECUTIVE SUMMARY

Substantial evidence supports a strong, positive, causal association between acetaminophen and Neurodevelopmental Disorders (NDDs)—particularly Attention-Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and their related symptoms. Acetaminophen is the most commonly used over-the-counter pain and fever medication taken during pregnancy, with over 50% of pregnant women using acetaminophen worldwide[1,2] In numerous, well-designed studies involving tens of thousands of participants—and hundreds of thousands overall—when pregnant mothers were exposed to acetaminophen, their children were diagnosed with NDDs, including ADHD and ASD, and/or symptoms consistent with those disorders, at higher rates than children of pregnant mothers who were not exposed to acetaminophen. It is rare that associations between an exposure to a substance and certain disorder(s) have been observed so consistently over time, over a variety of study designs, and in a variety of patient populations. In my opinion, this striking relationship—observed many times in the literature—is one that is most likely explained by prenatal acetaminophen exposure causing ADHD and ASD. I reach this conclusion after an extensive review of the scientific evidence and application of the commonly used Navigation Guide and Bradford Hill methodologies. I have also reviewed and rely upon the expert reports of Dr. Robert Cabrera, PhD (teratology), Dr. Brandon Pearson, MSc, PhD (toxicology), Dr. Eric Hollander, MD (neurodevelopment) and Dr. Stan Louie, PharmD (pharmacology) in reaching my opinion in this case.

Even before being retained as an expert in this case, I was involved in researching the relationship between in utero acetaminophen exposure and neurodevelopment. I led a large human study funded by the National Institutes of Health that investigated the impact of prenatal acetaminophen use during pregnancy on children's neurodevelopment. By 2019, multiple studies had shown an association between prenatal acetaminophen exposure and NDDs. That year, my co-authors and I published a small study that examined whether the levels of acetaminophen detected in fetal meconium were associated with reduced measures of child intelligence.[3] Although that study did not detect statistically significant results, its small size, focus on intelligence scores (rather than more direct measures of NDDs), and other limitations reduced its explanatory power. As a result, I continued researching this issue. In 2020, my co-authors and I published a paper in a respected medical journal, *JAMA Pediatrics*, showing an association between ADHD and the amount of acetaminophen observed in the child's meconium shortly after birth, an indicator of how much acetaminophen the child was exposed to while in utero.[4] After

being retained here, I was asked to perform an even more comprehensive review of the medical and scientific literature regarding the relationship between prenatal acetaminophen use and NDDs, including ADHD and ASD, and to opine as to whether or not the association is causal.

My opinion is that the association is causal, and I reached that conclusion by applying the same scientific methods I apply in my research and scientific practice.

As noted, one method I applied is the Navigation Guide, which has been recommended by the EPA to assess causal relationships for toxic substances, provides a systematic and rigorous approach to synthesizing evidence, and was established to more readily evaluate causal relationships for toxic and environmental harms. It requires a systematic rating and review of each identified study for bias, strength of evidence, and other indicia of study quality. The purpose of the Navigation Guide is ultimately to rate and assess the overall evidence and conclude whether the overall strength of the evidence makes the substance "known to be toxic," "probably toxic," "possibly toxic," "not classifiable," or "probably not toxic." To perform the analysis under the Navigation Guide, I first conducted a systematic literature search and reviewed and ranked the original studies. After reviewing the studies and ultimately assigning ratings, see attached Appendix 1, I concluded that acetaminophen is known to be toxic with regard to NDDs like ADHD and ASD.

The other method I applied is weighing and assessing the Bradford Hill factors/elements, which is the "canonical approach" for inferring causation and is "widely cited in the health sciences."[5] The nine, non-exclusive factors/elements considered under the Bradford Hill method to assess causation are: (1) strength of association, (2) temporality, (3) consistency, (4) biological plausibility, (5) coherence, (6) specificity, (7), experiment, (8) dose response (biological gradient), and (9) analogy.[6] It is not necessary to satisfy each factor to make a causal determination. Based on my review of the evidence, I determined that each of the factors was satisfied except for specificity. In my analysis, I assigned the most weight to dose response, consistency, and strength of association. I assigned moderate weight to biological plausibility. I also determined that the elements of coherence, experiment, and temporality were satisfied, though I placed less weight on those Bradford Hill elements (which is consistent with standard practice, as they are less probative on the question of causation.)

For example, regarding dose response, multiple studies, including the one I conducted, have demonstrated a clear dose response—*i.e.*, that increasing doses of in utero acetaminophen exposure led to increasing rates of neurodevelopmental outcomes, including ASD and ADHD, and related

symptomology, in children. These results provide strong evidence of a causal relationship. Nearly every study that evaluated a dose response found an association between the number of days of prenatal use of acetaminophen or cumulative dose and evidence of symptoms of NDDs in children.[2] These studies, including some that were able to more directly measure exposure levels by examining the acetaminophen content in meconium and umbilical cord blood, demonstrate that the higher the acetaminophen levels in the meconium and the cord blood, the higher the risk of the child ultimately being diagnosed with ASD or ADHD.[4]

Regarding consistency and strength, the strong association, observed between prenatal acetaminophen exposure and NDDs, including ADHD, ASD, and related symptomology, as well as other NDDs that share the same mechanisms of injury, has been replicated numerous times in the studies. Given this replication, which at this point has occurred more than 20 times – and *every* time in the highest quality studies—there is essentially no possibility of these findings being due to chance. As one 2018 review put it after reviewing nine, large cohort studies, "*all* included studies suggested an association between prenatal exposure and neurodevelopmental outcomes."[7] There have been numerous studies since 2018 that are consistent with that result as well.

Further, what is scientifically known both about the pharmacology of acetaminophen and about the developing fetal brain strongly support the association being causal, which satisfies the biological plausibility factor. The fetal brain and nervous system are exceptionally vulnerable to injury during critical prenatal periods of neurodevelopment. Studies have shown that multiple different environmental factors and insults can affect and alter normal development leading to neurodevelopmental outcomes. Given its known and accepted mechanisms of action, it is plausible that acetaminophen would have a substantial effect on fetal neurodevelopment.

Finally, a causal relationship is consistent with the fact that, as acetaminophen has become the recommended pain reliever for pregnant mothers, the rates of ADHD and ASD have increased more than 20-fold over the past decades. Multiple researchers have suggested that in utero acetaminophen use might explain the marked increase in ASD and ADHD rates observed in recent years. For example, the authors of the Shaw study stated that "[t]he marked increase in the rate of autism [and] attention deficit with hyperactivity may be largely caused," at least in part, "by the marked increase in … the use of acetaminophen by pregnant women."[8] The authors of the Liew et al. (2014) study stated that, although further study was needed, the observed association between in utero APAP exposure and ADHD "might

explain some of the increasing incidence in HKD [hyperkinetic disorder]/ADHD" over the past decades.[9] These statements, which are alarming, only make sense if there is in fact a causal relationship at work.

My opinion based on my Navigation Guide and Bradford Hill assessments, either of which would be sufficient to determine a causal association, is that there is a causal relationship between prenatal acetaminophen use and the NDDs of ADHD and ASD and the related symptomology.

Causation is by far the most likely explanation because the other explanations are less plausible. When researchers detect an association between an exposure and a disease, there are three theoretical possibilities: (1) The association could be causal. (2) The association could be due to chance – a statistical anomaly. (3) The association could be due to bias, particularly confounding – for example, there is a strong association between hair color and death rates, which is driven by the fact that age is correlated with both gray hair and mortality, not that hair color causes death.

There are no alternatives other than these three possibilities. Once chance and bias are ruled out, causation remains the only explanation. And here, as other authors have noted, "several lines of reasoning suggest that bias, confounding and chance are not solely responsible for the observed relationships."[7] That leaves causation as the most likely—indeed the only—explanation for the association. As one study put it (quoting the Bradford Hill methodology and Sherlock Holmes), "Once you have eliminated the impossible whatever remains, no matter how improbable, must be the truth."[10]

As for chance, the association between prenatal acetaminophen exposure and NDDs cannot be due to random noise in the sample populations studied. It has been replicated far too many times. Although the result of a single study might occur due to chance, that is almost impossible when the result occurs more than 20 times.

There is also no credible evidence that confounding or other forms of bias are responsible for the association. Despite numerous attempts to show that bias and confounding might be responsible for the link between prenatal acetaminophen exposure and NDDs, the association has persisted. As one paper put it, researchers have applied numerous methodologies trying to "make the association 'go away.'"[10] But it has not gone away. Attempts to provide evidence for alternative explanations—other than causation—"have so far been unsuccessful" despite many, many attempts.[10]

Taken as a whole, the epidemiology studies discussed in this report controlled for measurable confounders and attempted to account for the possibility of unmeasurable or residual confounding. To attempt to rule out the possibility of confounding—as seen with hair color and mortality—the studies

controlled for factors that might be correlated with acetaminophen use and also correlated with NDDs. To do so, the studies controlled for maternal age, maternal illness, maternal use of medications, maternal intelligence, parental education levels, child birth weight, child gestational age, socioeconomic status, maternal drinking, maternal smoking, maternal drug use, genetic confounding, confounding due to indication (*i.e.*, the clinical reason for taking the medication), and many other potential risk factors. The association persists despite controlling for those confounders. In other words, even after controlling for whether the mother smoked, drank, was from a lower socioeconomic status, and so on, a child who was exposed to acetaminophen in utero still had a higher risk of developing neurodevelopmental symptoms and/or being diagnosed with ADHD and/or ASD than a child who was not exposed. The strengths of these controls provide strong evidence that the observed relationship is not confounded, but in fact a causal one.

In addition, many of the studies also employed innovative study designs to assess whether any unmeasured or residual confounders might be driving the observed association. For example, some of these studies showed that acetaminophen use *before* pregnancy is not associated with markers of neurodevelopmental problems (even though acetaminophen use *during* pregnancy is).[11,12] Other studies showed that acetaminophen use *after* pregnancy is not associated with markers of neurodevelopmental problems (even though acetaminophen use *during* pregnancy is).[12,13] Still other studies showed that the use of other pain relievers (like ibuprofen) during pregnancy were not associated with neurodevelopmental outcomes even though acetaminophen was—in other words, they showed an effect specific to acetaminophen itself.[14,15] Importantly, despite all innovative designs and adjustments to address and control for confounding, the observed association between acetaminophen and neurodevelopmental outcomes persisted. This provides powerful evidence against the idea that the association here can be explained away by any sort of confounding.

Given the breadth of indications for APAP in pregnancy, and the statistical signal picked up in many studies despite a great deal of "noise" in the data (which would dampen the true association), the confounder for consuming APAP would have to have *enormous* power in order to explain the association. Although the makers of Tylenol have suggested that fever or other maternal infection may be the explanation, the relative risk of those conditions perturbing neurodevelopment combined with the relatively low number of women taking APAP for those conditions while pregnant—8% of women take acetaminophen for fever according to one study[16]—means that the mathematics simply do not add up.

I am not alone in believing that causation is the most likely explanation for why women who take acetaminophen while pregnant have children diagnosed with ADHD and ASD at higher rates than women who do not take acetaminophen while pregnant. There are many other researchers who, though acknowledging the *theoretical* possibility of alternative explanations, have suggested that causation is on balance the most likely one. For example, the authors of the Olsen and Liew paper noted that recent research—including data from several cohorts from around the world—has "increased the probability that the association is causal."[10] The authors of the Gou study concluded that, though not definitive, the epidemiology findings thus far "lend weight to the hypothesis that the association is causal."[17] The authors of the Ystrom study concluded that one set of their results were "consistent with a causal link."[11] The authors of the Stergiakouli study noted that their findings (combined with previous ones) were "consistent with an intrauterine effect," *i.e.*, with causation.[13] And the authors of the Alemany study reviewed the Bradford Hill methodology for assessing causation—as I did below—and concluded that the "causal" elements of "biological plausibility," "coherence," "consistency," "temporality," and "dose response" have all been demonstrated.[18]

This suggestion of causation is not limited to academic papers; it has made its way into the textbooks as well. The Briggs *Drugs in Pregnancy and Lactation* textbook—which is considered an authoritative "reference guide to fetal and neonatal risk"—provides "pregnancy recommendations" designed "to assist the reader in determining the level of risk of a specific drug."[19] For acetaminophen, the Briggs textbook's pregnancy recommendation states that "long-term use suggests risk." The textbook goes on to state that "although originally thought not to *cause* harm, this assessment must *change* because of recent data" linking several weeks' worth of prenatal acetaminophen use to "decreased IQ, ADHD, and other problems in neurodevelopment." The textbook concludes that, although "the drug should not be withheld if required for maternal fever," "routine use of acetaminophen should be avoided" by pregnant women.

Nor am I alone in believing that confounding cannot explain the repeatedly observed relationship between in utero acetaminophen exposure, ASD, and ADHD. For example, the authors of the Bornehag study (citing a recent review) noted that "confounding alone is an unlikely explanation for the associations reported in these studies" and that "our available data do not support confounding by indication."[20] The authors of the Alemany study noted that "the consistent associations" make it "unlikely that the observed relationship between prenatal acetaminophen and [ASD] and ADHD symptoms is entirely explained by unmeasured confounding."[18] The authors of the Gou study state that

"[i]t is overly simplistic and not justifiable to explain away the possibility of causality through confounding factors alone."[17] The authors of the Ricci study stated that "[c]onfounding by indication did not explain the association between in utero acetaminophen exposure and child ADHD."[21] The authors of the Khan review stated that they did "not see the confounding effects of other risk factors for neurodevelopmental disorders."[22] The authors of the Olsen and Liew paper stated in no uncertain terms that "it is too simple and not justified to explain away the possibility of causality by mentioning confounding."[10] And the authors of the Bauer and Kriebel paper state that "bias, confounding, and chance are not solely responsible for the observed relationships."[7] That leaves causation as the explanation.

In sum, application of the Navigation Guide methodology and the Bradford Hill factors to the scientific literature show there is likely a causal link between exposure to acetaminophen during pregnancy and offspring suffering from a NDD, including ASD and ADHD, and the related symptomology. Simply put, that means it is likely acetaminophen has caused scores of children to develop symptoms of and/or be diagnosed with NDDs including ADHD and ASD. Taking appropriate steps to advise pregnant women to limit the amount of acetaminophen they consume is a public health imperative with enormous ramifications. As a scientist who has extensively investigated the impact of prenatal and early life exposures on children's health, I view acetaminophen usage during pregnancy as a modifiable risk factor that women and doctors should be warned about because of the substantial risk to children's health.

In this view as well, I am not alone. The Olsen and Liew study authors recommended that "mothers-to-be should at least be advised to avoid the drug if treatment is not necessary for her conditions."[10] The Bauer and Kriebel paper concluded that "the time has come for some precautionary action" and that "pregnant women should be cautioned against indiscriminate use of this medication [acetaminophen]."[7,1] The Masarwa study authors have stated that "[c]areful inspection of current health policies and patient leaflets is needed."[24] The Alemany study authors stated that although acetaminophen should not be suppressed, it nevertheless "should be used only when necessary" by pregnant women.[18] The Thompson study authors suggested "efforts to inform the general public of the newly identified risks of this commonly used over-the-counter drug."[15] The authors of the Patel review recommended "timely appropriate labeling updates" be made for the benefit of "consumers and healthcare providers."[25] And the authors of the Bauer consensus statement – a collection of "91

[redacted]

scientists, clinicians, and public health professionals from across the globe"—recommended "that pregnant women should be cautioned at the beginning of pregnancy to: forego APAP unless its use is medically indicated . . . and minimize exposure by using the lowest effective dose for the shortest possible time."[2]

B. INTRODUCTION

1. Mandate

I have been retained to review the current state of the epidemiological scientific literature to assess the influence of prenatal use of acetaminophen (also known as paracetamol) on the developing brain, and specifically to determine whether the prenatal use of acetaminophen causes NDDs including ADHD, ASD, and/or symptoms consistent with those disorders in the child. All my opinions in this report are based upon a reasonable degree of scientific and medical certainty.

2. Credentials, Expertise, and Experience

I am a Full Professor and Chair of the Department of Environmental Health Sciences at the Columbia University Mailman School of Public Health in the City of New York, one of the top four schools of public health in the country. I am also appointed as Professor in the Department of Epidemiology at the Columbia University Mailman School of Public Health. I have held these positions since 2016. Before joining Columbia University, I was an Associate Professor of Epidemiology and Environmental Health Sciences at Harvard University's T.H. Chan School of Public Health in Boston from 2010 to 2016.

Since 2017, I have also served as the Center Director for the NIEHS P30 Center for Environmental Health and Justice in Northern Manhattan, Columbia University—one of the 20+ centers nationwide investigating the effects of toxic chemicals on health—and the Director of the Skills for Health and Research Professional (SHARP) Program for Professional Education in Precision Medicine and Public Health at Columbia University. I am also the Chair of the Committee for the Use of Emerging Science for Environmental Health Decisions at the National Academy of Sciences.

My educational background includes an MD *summa cum laude* from the University of Perugia, Italy in 1995, followed by an MPH in Epidemiology *summa cum laude* from the University of Turin, Italy in 2000. I obtained my PhD in Toxicology and Occupational Health *summa cum laude* from the University of Milan, Italy in 2003. Additionally, I completed post-doctoral training in Genetic Epidemiology, Environmental Health and Toxicology at the National Institutes of Health in Bethesda, Maryland in 2005.

I currently serve as President of the International Society of Environmental Epidemiology, a position I have held since 2021. Since 2022, I have also served as the Chair for the Committee for the Use of Emerging Science for Environmental Health Decisions, National Academy of Sciences. I also served as the Co-Director of the Interdisciplinary T32 Training Program in Genes and the Environment from 2014 to 2016 at the Harvard T.H. Chan School of Public Health, and as the Director of the Interdisciplinary T32 Training in Environmental Health from 2016 to 2018 at the Columbia University Mailman School of Public Health. I currently serve as an Editorial Board Member of *Environmental Epigenetics*, since 2015, and *Journal of Applied Toxicology*, since 2012. I previously served as the Associate Editor of *Environmental Health Perspectives*, from 2013-2018.

I have published more than 600 peer-reviewed papers, including 249 over the past five years. I have published more than 50 peer-reviewed papers on the toxicology of drugs and chemicals on the human brain. In total, my publications have been cited 47,300 times in the scientific literature (H-index = 111.) I was included in the list of Highly Cited, World's Most Influential Researchers of the past decade by Web of Science in 2020. I have conducted extensive research on the effects of environmental toxins, including acetaminophen, on neurodevelopment. Specifically, I led a large human study funded by the National Institutes of Health that investigated the impact of prenatal acetaminophen use during pregnancy on children's neurodevelopment. I have published studies on the adverse effects of prenatal exposure to acetaminophen on children's neurodevelopment, respiratory health, and reproductive health. I have also examined the underlying mechanisms through which prenatal exposure to acetaminophen may lead to these adverse health outcomes. I have published numerous papers on neurodevelopmental outcomes in connection with environmental exposures as described more particularly in my CV which is attached to this report as Exhibit A. I have also published on causal relationships between environmental exposures and neurodevelopmental outcomes. My publications have included other concepts related to this report including oxidative stress, gene expression, epigenetic changes, and the manners in which we can use data to understand complex health risks.

For instance, in one of our recent papers[26], which was published in *JAMA Pediatrics* (one of the top pediatrics journals worldwide), we examined the association between prenatal acetaminophen exposure and ADHD in children aged 6 to 7 years, as well as the potential for mediation by functional brain connectivity—in other words, we examined whether prenatal acetaminophen exposure causes changes in brain connectivity that might then result in ADHD. We found that acetaminophen exposure detected in meconium was associated with increased risk of ADHD, with a dose-response association

detected. Specifically, children with acetaminophen detected in meconium showed increased negative connectivity between frontoparietal and default mode network nodes to clusters in the sensorimotor cortices, which mediated an indirect effect on increased child hyperactivity. In other words, we observed changes in brain activity in children who were exposed to acetaminophen in utero and ultimately developed ADHD.

I currently run the Laboratory of Precision Environmental Health at Columbia's Mailman School of Public Health where we, on a daily basis, investigate links between environmental exposures and health outcomes. We work with cohorts nationally and internationally to investigate how certain exposures impact health, especially in vulnerable populations including pregnant women. The lab also uses highly quantitative genome-scale technologies for DNA methylation analysis to examine DNA methylation responses to environmental pollutants to investigate disease mechanisms.

I have received numerous accolades for my contributions to the field of public health, including being elected to the National Academy of Medicine in 2020 for pioneering new approaches to identify and characterize chemical risks.

In summary, as a public health expert with a background in epidemiology and toxicology, I am qualified to provide expert testimony on the adverse effects of prenatal acetaminophen use on human health. My expertise is the identification and characterization of chemical risks and the effects of medications on neurodevelopment. My Curriculum Vitae sets forth my education, training, publications, and work history in greater detail.

3. Overall Approach

The foundation of this report is my extensive education, expertise, and years of experience in designing, conducting, analyzing, and interpreting epidemiological studies, along with my training in epidemiology and toxicology. I have utilized my decades of experience in analyzing and interpreting epidemiological studies to produce comprehensive reports for various organizations, including the Environmental Protection Agency, the National Institutes of Health, the National Academy of Medicine, and the European Union.

My opinions are rooted in my review of the peer-reviewed, published epidemiological evidence examining the association of prenatal exposure to acetaminophen in utero with neurodevelopmental outcomes including ADHD and ASD and the symptoms of those disorders. I analyzed original case-

control and cohort studies, but also include observations regarding relevant meta-analyses and systematic reviews. To evaluate the quality of the studies and the evidence regarding the relationship between prenatal exposure to acetaminophen and neurodevelopmental outcomes in children, I applied my expertise as a researcher. Specifically, I drew on my 20 years of experience as a PhD-trained epidemiologist and toxicologist and 28 years as an MD-trained clinical scientist. In addition to my review of epidemiological studies, I have also assessed evidence from animal toxicology studies and research concerning the mechanisms of prenatal acetaminophen exposure and its effects on the developing brain. I do not summarize those studies in my report, but I agree with the reviews provided in the reports of Dr. Cabrera and Dr. Pearson.

In developing my opinions in this report, I utilized and applied the same rigorous standards that I apply in my academic and research work.

C. METHODOLOGIES EMPLOYED TO ASSESS WHETHER ASSOCATION IS CAUSAL

In reaching my conclusions as to whether prenatal exposure to acetaminophen can cause NDDs, including ADHD and ASD, and the symptoms of those disorders, I utilized two peer reviewed and well-accepted methodologies, the Bradford Hill[6] and the Navigation Guide[27]. Bradford Hill is an accepted method for inferring causation from associations and is derived from Sir Austin Bradford Hill's seminal lecture in 1965. Over the past 30 years, new methods have been developed, like the Navigation Guide, to appraise the strength of evidence across multiple studies, including observational and preclinical studies, to assess a causal relationship. The Navigation Guide, for instance, was recommended by the Committee to Review EPA's Toxic Substances Control Act as an approach the EPA should use in evaluating TCPA risks.[28] Multiple approaches may be appropriate for determining causation in a specific situation, and while I have used different techniques over the course of my career, the Navigation Guide methodology in particular provides for a consistent and reliable approach in reaching causality conclusions and does not unduly emphasize RCTs when evaluating the strength of evidence.[27] The Navigation Guide was established to more readily address toxic and environmental causal relationships because RCTs are not often available to address these important health issues.[27] This is critical because "[t]here are far too many examples of environmental hazards that were permitted to be produced long after the evidence for harm was substantial" based on conventions of causal inference.[29] Both of these methodologies, the Bradford Hill Causality Assessment and the Navigation Guide, are methods I use in my daily practice as an epidemiologist and I know them to be reliable.

1. Navigation Guide Methodology and Analysis

a. Identification of Relevant Studies—Search Terms Used and Numbers and Types of Papers Retrieved

As part of this methodology, on March 19, 2023, I conducted a systematic search of the literature on PubMed to identify original papers on the relationship between ADHD, ASD, and NDDs and prenatal exposure to acetaminophen, including observational studies and meta-analyses. I triaged articles by title, then by abstract, and finally by complete paper. My search identified studies that found statistically significant increased risks of NDDs such as ADHD and ASD from prenatal acetaminophen exposure as well as a smaller number that did not. I excluded papers focusing on postnatal exposures from the results of the search. I identified additional, relevant studies in reviewing the results of my PubMed search. I subsequently confirmed that I had identified all relevant studies by querying ISI Web of Science and Google Scholar.

Original papers feature new data analysis and results from studies not published before. Therefore, they provide new information. I note here that during my review some authors appeared to have published essentially the same data from the same study more than one time—in this case, I reviewed both papers but focused more on the results from the most recent publication given the advances in data analysis and/or more complete data.

i. Acetaminophen and ADHD

For the first search on ADHD and acetaminophen, I used the search term "ADHD AND Acetaminophen." Using additional search terms, such as "Attention Deficit/Hyperactivity Disorder," "Paracetamol," or "Tylenol" did not return any more papers. The initial search yielded 74 papers. However, after refining the search to exclude papers not related to ADHD and prenatal acetaminophen exposure, I was left with 54 relevant papers. Of these 54 papers, 4 were in vitro or animal studies, 14 were original, non-duplicative studies in humans, 3 were meta-analyses, 23 were reviews or studies that duplicated or elaborated on previously published original studies in humans, and 10 were editorials or comments.

ii. Acetaminophen and ASD

Moving on to the second search on ASD and acetaminophen, I used the search term "(autism spectrum disorder OR autism OR ASD) AND (acetaminophen)." Using additional search terms, such as "Paracetamol" and "Tylenol," did not return any additional papers. The initial search retrieved 87 papers, but after removing papers that were not related to ASD and prenatal acetaminophen exposure, I

was left with 47 relevant papers. Of these 47 papers, 10 were in vitro or animal studies, 6 were original, non-duplicative studies in humans, 1 was a meta-analysis, 23 were reviews or studies that duplicated or elaborated on previously published original studies in humans, and 7 were editorials or comments.

iii. Acetaminophen and Other Neurodevelopmental Deficits/Disorders

Finally, for the third search on neurodevelopment and acetaminophen, I used the search term "(Neurodevelopment OR neurodevelopmental disorder OR brain development) AND acetaminophen." Using additional search terms, such as "Paracetamol" and "Tylenol," did not return any additional papers. The initial search yielded 262 papers, but to avoid overlap with the previous searches, I excluded papers that were related to ADHD or ASD. I also removed papers that were not related to neurodevelopment and prenatal acetaminophen. I was left with 37 relevant papers, including 13 in vitro or animal studies, 15 original studies in humans, 5 reviews, and 5 editorials or comments.

b. Extraction of Important Study Information

I used the standardized methodology of the Navigation Guide to extract and evaluate data from studies, using a data extraction table (attached as Appendix 1) to record important information from each study. As recommended by the Navigation Guide, for each study I recorded the publication year, study design, number of cases, number of controls (for case-control studies), total sample size (for cohort studies), population type, country, risk estimates, confidence intervals, and the type of NDD. I also indicated whether exposure-response relationships were assessed, the method used, and the results. After extracting the data, I evaluated and synthesized the papers to identify patterns, themes, and trends across the studies. This involved comparing and summarizing the extracted data and identifying similarities and differences between the studies. Information regarding study methods and main study results is described more fully below. I did not perform a new meta-analysis myself because excellent meta-analyses have been recently published.

c. Method to Assess of "Risk of Bias" According to the Navigation Guide

Next, using the Navigation Guide methodology, I assessed the risk of bias within each study. "Risk of bias" is defined in the GRADE system (Grading of Recommendations Assessment, Development and Evaluation), which is another systematic approach to grade quality of evidence, as characteristics of a study that can introduce systematic errors in the magnitude or direction of the results.[1] I classified each

of the observational studies identified in the three categories of PubMed searches identified above by addressing the following questions:

i. Selection: Was the strategy for recruiting participants consistent across study groups?

When assessing the risk of bias in a study, one important factor to consider is whether the strategy for recruiting participants was applied consistently across study groups. I reviewed each of the studies using the below criteria and ratings scale.

I rated as "low risk of bias" (score = 1) those studies that applied recruitment and inclusion/exclusion criteria similarly across study groups and recruited study participants from the same population and at the same time frame.

I rated as "probably low risk of bias" (score = 2) those studies where there was incomplete information about participant selection to permit a rating of "low risk of bias," but there was enough direct or indirect evidence that suggested that participant recruitment and inclusion/exclusion criteria was consistent, as described above.

I rated as "probably high risk of bias" (score = 3) those studies where there was insufficient information about participant selection to permit a rating of "high risk of bias," but there was indirect evidence that suggested that participant recruitment or inclusion/exclusion criteria was inconsistent across study groups.

I rated as "high risk of bias" (score = 4) those studies where there was insufficient information about participant selection to permit a rating of "probable high risk of bias," where there was evidence of any of the following: a. protocols for recruitment or inclusion/exclusion criteria applied differently across study groups; b. study participants recruited at different time frames; c. study participants recruited from different populations and proportions of participants from each population in each study group are not uniform; d. differential loss to follow-up between groups; or e. reported refusal/non-response different between groups

ii. Blinding: Was Knowledge of the Group Assignments Inadequately Prevented (*i.e.*, Blinded or Masked) During the Study, Potentially Leading to Subjective Measurement of Either Exposure or Outcome?

While investigators are required to be blinded to the randomization group in clinical trials, investigators are typically unblinded in epidemiology studies. Indeed, knowledge of the exposure and outcome is

required to conduct a statistical analysis of observational data, such as for instance to select potential confounders. Indeed, none of the studies evaluated reported any information about investigators being blinded. However, one important source of bias in observational studies stems from recall bias (see section F.1.m.), which is caused by the participants being aware of the outcome. Recall bias may occur when information about prenatal acetaminophen use is collected after the informant (typically the mother) is aware that the child developed an NDD, including ASD or ADHD.

iii. Exposure: Were Exposure Assessment Methods Lacking Accuracy?

I also considered whether exposure assessment methods were accurate in assessing bias. For studies that did not rely on self-reporting, I assigned a low risk of bias (score=1). For studies that relied on self-reporting but were provided during pregnancy or shortly after delivery, I rated those studies as "probably low risk of bias" (score = 2). I took into account instances where maternal self-reports appeared to be of lower quality, such as where interviews were delayed, and assigned those studies a higher risk of bias depending on the quality (score= 3 or 4).

iv. Outcomes: Were Outcome Assessment Methods Lacking Accuracy?

Clinical assessment and diagnosis of ASD, ADHD, and other NDDs rely on a battery of neuropsychological tests and information reported by the child's parents and teachers, as indicated in section D.3.a. To assess the accuracy of outcomes, I evaluated whether the approaches used to identify these outcomes were appropriate. I also used indirect post-hoc evidence of the overall rates of outcomes in a study; if the rates differed substantially from those expected, I considered that difference derived from limitations in outcome assessment. Finally, a minor weakness in some studies was their assessment of outcomes in younger children, when symptoms may have not yet (fully) developed. ASD and ADHD prevalence increases as children grow older; according to recent data by the Centers for Diseases Control.[30] For example, only 2% of children aged 3-5 years are diagnosed with ADHD in the U.S. relative to 10% at age 6-11 years and 13% at age 12-17 years. Therefore, I considered the child's age at the time of evaluation or diagnosis when rating outcomes.

I used the following scores to rate outcome assessments:

I rated at "low risk of bias" (score = 1) studies that used appropriate methods for capturing symptoms or diagnosis of outcomes and did so at an appropriate child age.

I rated as “probably low risk of bias” (score = 2) studies that used validated tests that have lower predictive value; or – for ADHD studies – when they performed assessments in children between 3-5 years of age. While ADHD diagnosis can be accurately made in 3-5 year-old children, many children may have not yet developed symptoms. Therefore, at this age children who will eventually develop ADHD may be included in the non-ADHD outcome category, a situation that is likely to dilute a possible association with prenatal acetaminophen.

I rated as “probably high risk of bias” (score = 3) studies that did not use a standard assessment of outcomes to evaluate the outcome, provided the assessment was validated; or those that used a standard approach to outcome assessment but reported rates of outcomes very different from those expected in the age range of the children at the time of assessment, hence indicating probable issues with the implementation of outcome assessment in the study.

I rated as “high risk of bias” (score = 4) studies that did not use a validated assessment of the outcome measured or presented evidence suggesting that the assessment was performed inappropriately.

v. Confounding: Was Potential Confounding Inadequately Incorporated?

I rated as low risk of bias (score = 1) studies that considered and appropriately adjusted for confounding by indication as well as other possible relevant confounders.

I rated as “probably low risk of bias” (score = 2) studies that adjusted for multiple potential confounding variables but did not assess/control for confounding by indication.

I rated as “probably high risk of bias” (score = 3) studies that did not evaluate a comprehensive list of confounders.

I rated as “high risk of bias” (score = 4) studies that did not consider/adjust for confounding variables or used inappropriate methods for confounding control.

vi. Incomplete Data: Were Incomplete Outcome Data Inadequately Addressed?

The studies that I reviewed employed various methods to address incomplete data, such as imputation and multiple imputation of missing data. These methods allowed the researchers to make informed estimates of missing values, which can help to reduce bias in the study's findings. Furthermore, most of the studies reported that missing data were of low frequency, which suggests that the overall impact on the study's conclusions was likely minimal. Overall, by using appropriate methods such as imputation

and multiple imputation, and reporting low frequency of missing data, these studies demonstrated a strong commitment to rigorous research methodology and high-quality data analysis.

I rated as low risk of bias (score = 1) studies that showed no evidence of incomplete outcome data or handled incomplete data appropriately.

I rated as "probably low risk of bias" (score = 2) studies that that showed evidence of incomplete data and provided insufficient handling of incomplete data.

I rated as "probably high risk of bias" (score = 3) studies that showed evidence of substantial incomplete data (>30%) and provided insufficient handling of incomplete data.

I rated as "high risk of bias" (score = 4) studies that had more than 50% incomplete data and provided insufficient handling of incomplete data.

vii. Selective Reporting: Does the Study Report Appear to Have Selective Outcome Reporting?

In order to evaluate the reliability and validity of a research study, it is important to assess whether the study report appears to have selective outcome reporting. Selective outcome reporting occurs when the results that are reported in a study are biased due to the selective inclusion or exclusion of certain outcomes or data. Because selective reporting can either occur or not, I only used two binary levels to rate this category:

I rated as low risk of bias (score = 1) studies that showed no evidence of selective reporting.

I rated as "probably low risk of bias" (score = 2) studies that showed evidence of selective reporting.

viii. Conflict of Interest: Did the Study Receive any Support from a Company, Study Author, or Other Entity Having a Financial Interest in any of the Exposures Studied?

Based on my review of the studies, there was no evidence that the authors received support from a company, organization, or other entity having a financial interest related to the study questions. I specifically reviewed the funding or sponsorship of each study. However, it is important to note that the absence of evidence of a conflict of interest does not necessarily guarantee the absence of any such conflict and my review is limited to the information available through the authors' disclosures.

Because conflict of interest can either occur or not, I only used two levels to rate this category:

I rated as low risk of bias (score = 1) studies that did not present any evidence of conflict of interest.

I rated as "probably low risk of bias" (score = 2) studies that presented evidence of conflict of interest.

ix. Other Sources of Bias: Did the Study Appear to Have Other Problems that Could Put It at a Risk of Bias?

When evaluating the reliability of a research study, it is important to assess whether the study appears to have any other problems that could put it at a risk of bias beyond the eight components already reviewed. These other sources of bias could potentially impact the study's validity and reliability. I determined that, whenever I found an issue to be included in this category, I would use a rating from 1 to 4 based on my assessment of the severity of the issue.

Before beginning my review, I predetermined how to apply the nine elements of the risk-of-bias assessment to evaluating the associations between prenatal acetaminophen and ADHD, ASD, and other neurodevelopmental deficits/disorders. As recommended by the Navigation Guide, I classified all observational studies according to these nine questions using the following scores: 1. Low Risk of Bias; 2. Probably Low Risk of Bias; 3. Probably High Risk of Bias; and 4. High Risk of Bias. For each study, I averaged the nine scores to a summary score, which represents the overall risk of bias for each study.

d. Method to Grade the Strength of the Evidence of Each Study According to the Navigation Guide

Next, utilizing the Navigation Guide methodology, I graded the strength of evidence of each study. The Navigation Guide recommends beginning the evaluation of the strength of evidence of each observational study by assigning a preliminary "moderate" quality rating. This initial quality rating of "moderate" is independent of the specifics of each study, but the actual quality of the body of human observational studies is then accounted for through upgrading or downgrading the "moderate" rating based on a priori criteria. This differs from other systematic review frameworks focused on the clinical sciences, such as Cochrane and GRADE, which assign an a priori rating to the body of human observational studies of "low" quality based on an assumption that an RCT will be part of the available evidence.

The Navigation Guide, however, recognizes observational studies as reliable sources of evidence in the clinical sciences because not all health care decisions are, or can be, based on RCTs. Moreover, recognition of the absolute value of human observational data to evidence-based clinical decision making is increasing. There are several reasons for this. For example, the speed and complexity with

which new medical interventions and scientific knowledge are being created make it unlikely that the evidence base required for treatment and cost-effective health care delivery across subpopulations can be built using only RCTs. It is also expected that electronic medical records will revolutionize medical research by facilitating comprehensive, longitudinal observational data in an instant. Finally, and perhaps most important in the case of prenatal acetaminophen use, ethical considerations virtually preclude experimental human data. Therefore, relative to the evidence available for decision making in toxicology, and given the unavailability of RCTs, human observational studies are the "gold standard" of the evidence base.

Based on standard approaches used by both the Navigation Guide and GRADE and using the worksheet and criteria reported in the Navigation Guide example shared by Chiu et al. (2017),[31] I rated the strength of the evidence for each observational study based on the below criteria, and to ensure consistency and accuracy in my evaluations, I predetermined my approach across the six factors as follows.

i. Size: To evaluate the contribution provided to the strength of evidence by the size of the cohort, I assigned a score of 0 to studies that had a sample size between 500-999 participants. I upgraded the score to +1 if the sample size was between 1000-4999 and to +2 if it was 5000 or more. Conversely, I downgraded the score to -1 if the sample size was between 250-499 participants, and to -2 if it was less than 250 participants. For categorization of case control studies, I divided cohort range by 10 for case control sample size.

ii. Large effect: To evaluate the presence of a large effect, I assigned a score of 0 to studies that had a relative risk between 1.0-1.5. I upgraded the score to +1 if the relative risk was between 1.5-2.0 and to +2 if it was 2 or higher. I downgraded the score to -1 if the association between the injury and prenatal acetaminophen was not significant, regardless of the effect size, and to -2 if it were to be significant and with a relative risk lower than 1.00 (*i.e.*, protective effect of prenatal acetaminophen and the injury.)

iii. Exposure-response relationship: Regarding the exposure-response relationship, I assigned a score of 0 if there was no evidence of such a relationship. However, if there was evidence of an exposure-response relationship, I upgraded the score to +2. Because the exposure-response relationship can either be present or not present, I only used two of the five scores on the scale.

iv. Internal consistency: Internal consistency refers to the degree to which the results of a study are internally coherent and support the conclusions drawn from the data. To

evaluate internal consistency, I examined whether the results were consistent with the study hypothesis, research question, and the data collected. If the study reports only an individual result, I assigned a score of 0. If there were some inconsistencies or lack of clarity in the results, I downgraded the score to -1, and if there were major inconsistencies or contradictions, I downgraded the score to -2. If there were multiple results that showed moderate/medium consistency, I upgraded the score to +1, and if there were high levels of consistency, I upgraded the score to +2.

v. Control of bias: To evaluate the control of bias in a study, I examined whether the researchers had taken appropriate steps to control for potential sources of bias, such as selection bias, measurement bias, and confounding through the risk of bias assessment described above. If the study was well-designed and executed, I assigned a score of 0. If there were minor issues with controlling for bias, I downgraded the score to -1, and if there were major issues, I downgraded the score to -2. One special consideration I took into account was whether the study included strong consideration of confounding by indication; if confounding by indication was considered and addressed properly in the analysis, I upgraded the score to +1.

vi. Other factors: In addition to the previous criteria, I decided to include in the grading other factors that might not be included in any of the categories above. Similar to the other categories, I determined to use a scale ranging from -2 to +2 using a qualitative assessment to assign the scores.

As indicated in the table below, I used a score of 0 as the initial score which indicates moderate evidence. I upgraded the score to + 1 (strong evidence) or +2 (very strong evidence) if the study had strengths that positively modified the initial score. Conversely, I downgraded it to -1 (weak evidence) or -2 (very weak/no evidence) if the studies had weaknesses that negatively modified the initial score. The extent of downgrading/upgrading depended on predetermined cutoff for criteria that can be quantitatively assessed (reported in the corresponding tables, attached as Appendix 1) and on expert judgment for criteria that require qualitative assessments. As recommended, I summed all the scores across the nine criteria and obtained a final score that reflected the strength of evidence contributed by each individual study.

Table - Grading of Strength of Evidence of Each Study

Score	**Strength of evidence**
+2	Very strong

+1	Strong
0	Moderate
-1	Weak
-2	Very weak/none

The ratings of the separate factors are not added together into a score, *e.g.* a -1 downgrade for inconsistency and a -1 downgrade for control of bias does not automatically dictate an overall -2 downgrade for the body of evidence. Rather, according to the Navigation Guide, the final grading of each study is based on expert judgment to determine if the rationale behind each downgrade warrants an overall downgrade of 1 or 2 levels. The same applies to upgrading the overall body of evidence. Likewise, a -1 downgrade for one factor and a +1 upgrade for another factor do not automatically cancel out and determine no downgrades or upgrades for the overall body of evidence.

The results of these assessments are included in Appendix 1.

e. Expert Opinion Score on the Overall Quality of Each Study According to the Navigation Guide

Because some weaknesses of a study can be particularly damaging and contribute more heavily to the quality of the study, the Navigation Guide also recommends that each study is given an expert opinion score, which may more heavily weigh one or more criteria over the others. I therefore assigned my "expert opinion scores" also using the same scale from -2 to +2 and noted the rationale, when applicable, for assigning more weight to certain criteria. Note that the expert opinion score reflects the quality of the study and is typically heavily driven by strengths and weaknesses of the study and should be evaluated in parallel to the strength of the evidence score.

To ensure that my evaluation of the strength of evidence provided by each study investigating the link between prenatal acetaminophen use and NDDs was balanced and accurate, I predetermined a systematic approach, which I have found balanced and helpful in previous evaluations I performed using the Navigation Guide. I began by considering the sum of the scores across the six predetermined criteria, which included size, large effect, exposure-response relationship, study design, consistency, and precision. Based on the sum of these scores, I established a grading system. A sum of 8 or higher would receive a starting grade of +2, a sum between +3 and +7 would receive a starting grade of +1, a sum

between -2 and +2 would receive a starting grade of 0, a sum between -3 and -7 would receive a starting grade of -1, and a sum of -8 or lower would receive a starting grade of -2.

I found that this approach provided a more balanced initial score of the strength of evidence compared to taking the mean of all studies. This is because not all factors receive the full range of scores, so the mean tends to be tightly clustered around the 0 value and may differ significantly from a typical expert opinion score. Using this approach, I was able to evaluate the strength of evidence provided by each study systematically and objectively. However, I must clarify that I used these initial summary scores only as a guide reflecting the scores across the six factors. In other words, the summary scores informed my decision of the final expert opinion scores, but were not binding, as required by the Navigation Guide. This approach allowed me to make informed decisions about the quality of evidence provided by each study and draw more accurate conclusions about the link between prenatal acetaminophen use and the questions posed.

2. Bradford Hill

The Navigation Guide is a peer-reviewed, standardized, evidence-based approach to summarizing the evidence. Traditionally, however, epidemiologists have addressed the questions about whether a reported association is causal using the Bradford Hill methodology. The ultimate purpose of the Bradford Hill methodology is to allow scientists to use their judgment based on defined nonexclusive factors to be assessed when determining whether there is "any other answer equally, or more, likely than cause and effect."[6]

This is the "canonical approach" to making a "causal inference"—one that is "widely cited in the health sciences."[5] Hill based his factors to consider on "an earlier list published in the landmark U.S. Surgeon General's report Smoking and Health," which used causal inferences from epidemiology to link smoking to lung cancer.[5] As a recent review put it, "[t]he Bradford Hill Criteria remain one of the most cited concepts in health research and are still upheld as valid tools for aiding causal inference."[32]

Researchers employ the Bradford Hill factors after observations "reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance."[6] That is the case for acetaminophen and NDDs, as the studies cited in Section G as well as my Navigation Guide analyses make clear. The Bradford Hill factors provide factors to consider when "deciding that the most likely interpretation" of an association "is causation." Hill explained his methodology and

offered the following nine (non-exclusive) elements—none of which is individually necessary before making a causal inference—which should be considered in assessing causation:

a. Strength of Association

The greater the magnitude of the association between the exposure and the outcome, the more likely a causal relationship exists. "A strong association can help to rule out hypotheses that the association is entirely due to confounding or other bias."[5] But Bradford Hill cautioned that this factor is not always determinative, because there are in fact some relationships that are truly causal but not large in magnitude. As he put it, "we must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so."[6] As a result, there is "no general rule for how large an association needs to be to meet this consideration," and attempts to require "sharp boundaries" "such as at a doubling of risk" are based on "fallacious arguments" which should not be followed.[5]

Bradford Hill was especially prescient on this point. As modern commentators have noted "there are many weaker associations that are generally agreed to reflect causal effects," including the link between "air pollution and mortality," "smoking and heart disease," and "environmental tobacco smoke [*i.e.*, secondhand smoke] and lung cancer."[5] Although relatively weak, these associations "are considered causal in part because they have been replicated in a variety of populations using different designs and in part because considerations other than strength," *i.e.*, the other factors identified below.

When evaluating the strength criterion, the modern approach is to consider both the magnitude of an association and its statistical significance: However, notably, "failure to mathematically demonstrate statistical significance in a single study does not preclude the possibility of a meaningful exposure—response relationship in reality."[32] And Bradford Hill himself cautioned against rejecting a causal association just because statistical significance was lacking, *i.e.*, deducing "'no difference' from 'no significant difference.'"[6]

Exposures that are common can cause high numbers of cases even with small relative risks:

Exposures that are common can cause high numbers of cases even with small relative risks because the prevalence of the exposure is high in the population. Because a large proportion of the population is exposed to the risk factor, even a small increase in risk can result in a large number of people being affected by the disease or condition due to the exposure.

For example, consider a hypothetical exposure such as air pollution, which is widespread in many populations. Air pollution increases the risk of multiple diseases, including lung cancer and chronic obstructive pulmonary disease, cardiovascular disease, and dementia. All these air-pollution-related diseases cause an increased risk of death due to air pollution exposure. The Lancet commission on air pollution and health estimated that air pollution caused 9 million deaths globally in 2019. This means that air pollution causes approximately 11.5% of all deaths worldwide every year.

However, air pollution has a very weak association with the risk of death. For instance, a classic meta-analysis authored by Harvard's Dr. Joel Schwartz reported a relative risk of 1.06 (RR = 1.06, 95% CI = 1.05-1.07) for an increase of 100 µg/m3 in total particle concentrations in ambient air. A relative risk of 1.06 indicates that there is only a 6% increase in the risk of death associated with the exposure. However, because most people globally are exposed to air pollution, the small relative risk associated with air pollution results in tremendously high numbers of deaths globally. Indeed, the World Health Organization (WHO) reported recently that as many as 99% of the world population breathes air that exceeds WHO air quality limits, and such exposure threatens their health.

Another example comes from the authoritative scientific journal The Lancet, which published in 2013 an analysis of the possible triggers of Myocardial Infarction (MI, best known as heart attack). MI is characterized by an extended subclinical phase leading to the sudden onset of life-threatening acute events. Acute MI is often preceded by specific triggers, which may include common activities such as alcohol consumption, heavy meals, physical exertion, and stressful events. This analysis showed that at the individual level, cocaine use was by far the strongest trigger of MI (OR=23.7, an extremely strong risk ratio). However, because of the low reported frequency in the community, only 0.9% of MI cases were estimated to be triggered by cocaine.

Conversely, the population burden of air pollution—a risk factor that shows small relative risks in relation to MI—was substantially higher. Particulate matter (PM) is the air pollutant most consistently associated with MI onset. The authors estimated that if the levels of PM in a hypothetical city were to be decreased by 30 µg/m3, 4.8% of MIs might be avoided or delayed. The proportion of cases attributed to air pollution was five times larger than that attributable to cocaine use, although the relative risk for the association of cocaine use with MI was approximately 450 times larger than that of air pollution. Despite the low relative risk (OR=1.05) associated with PM, the population benefit would be considerable because the entire community of this hypothetical city would be advantaged by the air

pollution reduction. In this analysis, air pollution was highlighted as one of the strongest triggers of MI, together with physical exertion and alcohol binging, despite its very weak relative risk in relation to MI.

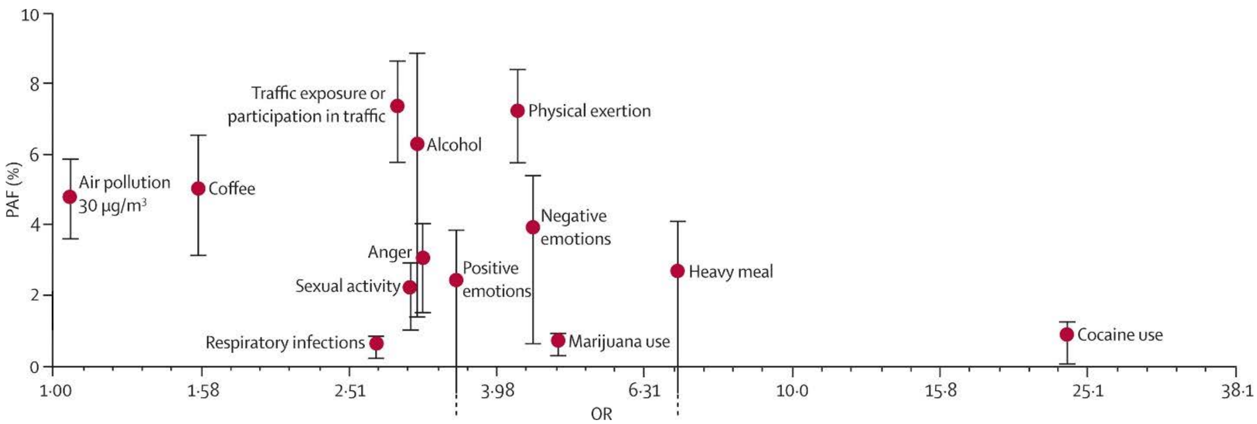


Figure 1: The graph shows the population attributable fractions (PAFs) for each of the major triggers of Myocardial Infarction (MI) in relation to the Odds Ratio (OR) linking triggers to MI. Air pollution is an example of a risk factor with a very small OR but responsible for a large number of cases.

Therefore, exposures that are common can have a significant impact on public health, even if the relative risk associated with the exposure is small. It is important to consider both the relative risk and the prevalence of an exposure when assessing its impact on the population.

b. Temporality

"Temporality means that a cause must precede its effects, and this is a necessary condition for valid causal inference."[5] When known, the exposure must precede the outcome in time: "which is the cart and which the horse?"[6] This criterion is typically used to rule out "potential reverse causation," whereby the outcome actually leads to the exposure.[5] For example, the number of umbrellas on a street is strongly correlated with whether it is raining, but the presence of the umbrellas does not cause the rain.

c. Consistency

"A consistent finding is an association reported across multiple populations, over time, and using different study designs."[5] The association between the exposure and the outcome observed across different populations, settings, and study designs supports a causal inference. In other words, "[h]as [the association] been repeatedly observed by different persons, in different places, circumstances and

times?"[6] "Traditionally, Hill's consistency criterion is upheld when multiple epidemiologic studies using a variety of locations, populations, and methods show a consistent association between two variables with respect to the null hypothesis."[32] In addition to human epidemiology, more basic research "can be integrated with the results of observational studies" in order to demonstrate consistency. "Consistency across studies of a similar design helps rule out chance as an explanation for an observed association."[5] Notably, a set of results is consistent even if some of the results are not statistically significant. Although "it is sometimes claimed that "a literature or set of results is inconsistent simply because some results are 'statistically significant' and some or not," this reasoning is "completely fallacious."[5] A set of results consistently showing a positive association between an exposure and a certain outcome is still consistent even if there are some results that are not statistically significant.

d. Biological plausibility

The existence of a biologically plausible mechanism to explain the association between the exposure and the outcome supports a causal inference. To establish biological plausibility, researchers look at "not only epidemiology," but also "other human studies, animal and tissue studies, and current understanding of the biology, pathology, toxicology, and other mechanisms related to the effect."[5] Bradford Hill noted that it was not always possible to "demand" this feature, because "what is biologically plausible depends upon the biological knowledge of the day."[6] As he recounts, true causal relationships (for typhus and rubella) were once ignored and doubted because the biological mechanism was not well understood at the time.

e. Coherence

When the association between the exposure and the outcome is consistent with existing knowledge about the disease, a causal inference is supported. "Hill used the term 'coherence' to mean that the hypothesized causal relation of exposure to disease does not conflict with current understanding of the disease process."[5] As he put it, a cause and effect interpretation "should not seriously conflict with the generally known facts of the natural history of the disease."[6] Hill offers the example of the "temporal rise that has taken place in the two variables [smoking and lung cancer] over the last generation," *i.e.*, the fact that smoking rates and lung cancer rates both increased at the same time was evidence of coherence—and thus evidence of a causal association between smoking and lung cancer.[6]

f. Specificity

"In Hill's formulation, specificity of an association can refer either to a cause having a single effect or an effect having a single cause."[5] When the exposure is associated with a specific outcome, causality is more strongly supported. In contrast, a non-specific association is one in which the exposure is associated with multiple outcomes, or the outcome is associated with multiple exposures. Bradford Hill cautioned that one should not "over-emphasize the importance of [this] characteristic."[6] Hill expressly offered his opinion that "one-to-one relationships are not frequent. Indeed, I believe that multi-causation is generally more likely than single causation, although, possibly if we knew all the answers, we might get back to a single factor. In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence."[6] Scientific developments since 1965 have shown Hill to be correct. For example, "even in the case of smoking and lung cancer," specificity is not satisfied.[5] And "indeed, many behavioral, environmental, social, and genetic risk factors have been linked to more than one health outcome," meaning that even in situations of known causality, specificity is not satisfied.[5] In part for this reason, under modern approaches, "[t]he original criterion of specificity is widely considered weak or irrelevant from an epidemiologic standpoint."[32]

g. Experiment.

Experimental evidence that manipulating the exposure leads to a change in the outcome can provide strong evidence for a causal relationship. In Bradford Hill's conception, "experiment" meant evidence "obtained from reducing or eliminating a supposedly harmful exposure and seeing if the frequency of disease subsequently declines."[5] Although Bradford Hill characterized this kind of evidence as "the strongest possible evidence of causality that can be obtained,"[5] he noted that this kind of evidence is only "occasionally" available at least in humans. But under more modern approaches, "[e]xperimental evidence can refer to clinical trials, to animal experiments, or to experiments on tissues."[5]

h. Exposure–response relationship.

Also known as "dose response" relationship and "biological gradient," exposure-response is particularly powerful evidence of causation when it is present. As Bradford Hill notes, "the fact that the death rate from cancer of the lung rates rises linearly with the number of cigarettes smoked daily adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers." A "clear dose-response curve" "puts the case for causation "in a clearer light."[6] In most cases, greater

exposure leads to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence. A "monotonic biological gradient, wherein increased exposure resulted in increased incidence of disease, provides the clearest evidence of a causal relationship."[32] But even a "nonmonotonic dose-response association" does not "refute causation" as "many substances display u-shaped or j-shaped dose response effects."[5]

i. Analogy.

"Analogy refers to drawing inferences about the association between a given exposure and disease based on what is known about other exposure-disease relations."[5] If the relationship between the exposure and the outcome is similar to the relationship between other exposures and outcomes, it may suggest a causal relationship. This is especially helpful when one member of a certain class of drugs is known to cause a certain disease—reasoning by analogy suggests other drugs in that class likely also cause the disease. "For example, based on what is known about the health effects of cigarette smoking, we might expect that inhalation of other combustibles (*e.g.*, marijuana) would have similar effects, even in the absence of studies on the subject."[5] And "the theory that the association of smoking with cervical cancer was at least partially causal became more plausible once it was accepted that smoking could cause cancer of the bladder, pancreas, and other organs not directly exposed to smoke."[5] This criterion need not be satisfied—and often is not. "Modern epidemiologists have argued that a lack of analogy does not preclude causation, but simply implies a lack of creativity on the researcher's part."[32] Indeed, the "absence of such analogies may reflect only lack of imagination or experience, not falsity of the hypothesis."[5]

As even Bradford Hill himself made clear, however, most of these single factors are not individually required to be satisfied before a researcher can reach a causal inference. "Hill's nine aspects of association were never intended to be viewed as rigid criteria or as a checklist for causation."[32] And "Hill also emphasized that causal inferences cannot be based on a set of rules" but instead must be done in a manner "more akin to clinical judgment."[5]

For example, Rothman notes that specificity, which evaluates whether the exposure is associated with the outcome of interest and not with other outcomes, often is not satisfied even when evaluating true causal associations. For instance, tobacco smoking is associated not only with a range of other cancers such as mouth and throat, voice box, esophagus, stomach, kidney, pancreas, liver, bladder, cervix, colon

and rectum, and leukemia, among others but also with non-cancer outcomes such as heart disease, stroke, lung diseases, diabetes, and chronic obstructive pulmonary disease (COPD), respiratory infections, certain eye diseases, autoimmune disease, and so on. Meanwhile, these cancers often appear in people who never smoked tobacco. As a result, tobacco smoke “typically lack[s] specificity when studied using classic epidemiology designs.”[32] Nevertheless, tobacco smoking is considered causally related to cancer even though the specificity element is not satisfied. As noted above, Bradford Hill himself cautioned strongly against placing weight on the absence of specificity: “if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.”[6]

Only the fourth element, temporality, is “indeed necessary (a sine qua non) for causal explanations of observed associations.”[5] If the putative cause did not precede the effect, that indeed is indisputable evidence that the observed association is not causal. This is “perhaps the only criterion which epidemiologists universally agree is essential to causal inference.”[32] Other than this one element, which may be viewed as part of the definition of causation, however, there are no “necessary and sufficient elements for determining whether an observed association is causal.”[5] The evidence must instead be judged as a whole across the other elements.

Causal inference is an essential aspect of epidemiology, as it provides critical information for identifying and preventing disease. However, it is important to note that establishing causality is complex and requires careful consideration of multiple factors, including study design, data quality, and potential confounding variables. But the ultimate purpose remains the same as what Bradford Hill suggested: To determine, based on all of the data, whether there is “any answer equally, or more, likely, than cause and effect.”[6]

D. BACKGROUND

1. Acetaminophen

a. Drug Profile

Acetaminophen, also known as paracetamol, is an active ingredient marketed for the relief of fever and pain in hundreds of over-the-counter (OTC) and prescription medicines. The best-known brand name of acetaminophen is *Tylenol®,* although the medication is available under a range of brand names and formulations*.* Acetaminophen can also be combined with other active ingredients in medicines that treat allergy, cough, colds, flu, and sleeplessness. In prescription medicines, acetaminophen is found

with other active ingredients to treat moderate to severe pain.[33] Acetaminophen was initially approved by the U.S. FDA in 1950 and has also been available for nonprescription OTC use since 1955.[34] It is available in a variety of forms including syrup form, regular tablets, effervescent tablets, injection, suppository, and other forms.[35]

Acetaminophen is rapidly absorbed from the gastrointestinal tract and reaches peak concentrations in the blood within 1 to 2 hours of ingestion. It is primarily metabolized in the liver by several different enzymes and is excreted primarily in the urine. The manufacturer claims, "The precise mechanism of the analgesic and antipyretic properties of acetaminophen is not established"; however, much is known about acetaminophen's mechanism of action. For one, acetaminophen inhibits the production of prostaglandins in the body, which are involved in pain and inflammation. Prostaglandins are produced by the body in response to injury or illness and can cause fever and pain. By inhibiting the production of these mediators, acetaminophen can help to reduce fever and alleviate pain.

In a 2011 alert, the FDA addressed the risk of acetaminophen-induced hepatotoxicity.[36] Administration of acetaminophen in doses higher than recommended or in therapeutic doses in susceptible persons may result in hepatic injury[37], including the risk of liver failure and death[38]; therefore, the maximum recommended daily dose of acetaminophen is not to be exceeded. The maximum recommended daily dose of acetaminophen includes all routes of acetaminophen administration and all acetaminophen-containing products administered, including combination products. [39] Acetaminophen may also rarely cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal.[40]

However, the potential adverse effects of prenatal acetaminophen on the developing brain are much more of a concern. For instance, unlike the liver, which can regenerate quickly and easily, the brain cannot regenerate lost neurons. Further, alterations in the normal processes of neurodevelopment can result in abnormalities that become fixed as the brain matures. This means that small insults caused by prenatal acetaminophen exposure can become persistent and have long-lasting neurocognitive effects. The developing brain is particularly vulnerable to environmental insults. Growing cells are more vulnerable to toxins which is significant because the brain forms over a longer period than do other organs.[41] Therefore, it is important to carefully consider the potential risks and benefits of prenatal acetaminophen use, particularly in light of the potential impact on brain development.

b. Mechanism of Action

Acetaminophen acts within the central nervous system to increase the pain threshold by inhibiting central cyclooxygenase, an enzyme involved in prostaglandin (PG) synthesis. Acetaminophen inhibits both isoforms of central cyclooxygenase, COX-1 and COX-2. Acetaminophen does not inhibit PG synthesis in peripheral tissues, which is the reason for its lack of peripheral anti-inflammatory effects.[42]

c. Pharmacokinetics

Acetaminophen can be administered orally, rectally, or intravenously. Acetaminophen is widely distributed throughout most body tissues except fat; low protein binding and molecular weight allow blood-brain barrier penetration. [39,43]

Postnatally, acetaminophen undergoes first-pass metabolism in the liver and is primarily metabolized through three separate pathways: glucuronidation, sulfate conjugation, and cytochrome P450 (CYP450) oxidation, specifically the enzyme CYP2E1. Glucuronidation and sulfate conjugation are the major routes of metabolism, while 5%-10%[44] of the drug undergoes oxidative metabolism via CYP2E1 producing the toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI).[45] It is important to note that CYP2E1 is not only present in the liver but also in fetal brains, placenta, and lungs.[46,47] This is concerning because as the developing brain of the fetus is particularly vulnerable to toxic insults, the presence of CYP2E1 in the fetal brain—as well as in other tissues—means that acetaminophen is metabolized in the brain to produce the toxic by-product NAPQI in the brain and other fetal tissues. At non-toxic doses, NAPQI is rapidly conjugated with glutathione (GSH) to form harmless metabolites, cysteine and mercapturic acid metabolites.[45] Acetaminophen at toxic doses, either due to supratherapeutic or repeated therapeutic doses, fasting, reduced or depleted GSH, alcohol use, or some combination of those factors, can lead to increased concentrations of NAPQI and resulting toxicity, most commonly hepatotoxicity.[43,48] The elimination half-life of acetaminophen is 2 to 3 hours in healthy adult patients.[39] Acetaminophen is renally excreted primarily as glucuronide conjugate (40% to 65%) and sulfate metabolite (25% to 35%). Mercapturic acid and cysteine metabolites account for 5% to 12% of the urinary metabolites; less than 5% is excreted as unchanged drug.[49]

d. Common Uses

In general, acetaminophen is used for the treatment of minor aches and pain and reduction of fever. Oral forms are the most common over-the-counter forms and the most widely used. Acetaminophen

injection[45] is indicated for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever. In adults, regular-strength acetaminophen is administered at 325mg to 650 mg orally/rectally once every 4 hours as needed not to exceed 3250 mg/day. Under supervision of healthcare professionals, daily doses of up to 4000 mg/day may be used. For extended-release capsules, two capsules (1300 mg) can be administered orally once every 8 hours as needed, not to exceed 33,900 mg/day.[50]

e. Adverse Effects

Acetaminophen toxicity can cause liver damage or even liver failure and can be life-threatening. Additionally, individuals with liver disease or allergy to acetaminophen are typically advised to consult a healthcare provider before taking this medication.

i. Hepatotoxicity

Acetaminophen use has been linked to liver failure, the need for liver transplantation, and death. The hepatotoxicity occurring with acetaminophen use typically correlates with high doses of acetaminophen that exceed the recommended maximum dose.[51,52] However, acetaminophen has been shown to produce some sequelae of hepatotoxicity even at therapeutic doses.[53] Liver damage also has been seen in patients with chronic dosing of acetaminophen or at indicated doses combined with high alcohol intake.

ii. Other Adverse Effects

Other adverse effects of acetaminophen administered orally or rectally may include the following:

1. Skin rash, hypersensitivity reactions
2. Nephrotoxicity (elevations in BUN, creatinine)
3. Hematological: anemia, leukopenia, neutropenia, pancytopenia
4. Metabolic and electrolyte
    1. Decreased serum bicarbonate
    2. Decreased concentrations of sodium and calcium
    3. Hyperammonemia
    4. Hyperchloremia
    5. Hyperuricemia
    6. Increased serum glucose

Additional adverse effects of acetaminophen administered intravenously include nausea, vomiting, constipation, pruritus, and abdominal pain.

Rare but serious adverse effects include hypersensitivity, anaphylactic reactions, and serious and even fatal skin reactions. These include toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome.[54]

f. Use of Acetaminophen During Pregnancy

Acetaminophen has never been subject to preclinical testing for neurodevelopmental outcomes[55] but is nevertheless currently considered the only pain and fever reducer indicated for use during pregnancy because of the risks of miscarriage or birth defects associated with other analgesics like ibuprofen or NSAIDs.[18] Therefore, acetaminophen has become the first line medication for fever and pain during pregnancy, leading to widespread use.

It is estimated that more than 60% of women use acetaminophen during pregnancy[16], and one study reported that 65% of pregnant women take acetaminophen.[56] According to one study, almost 20% of pregnant women use acetaminophen for more than 20 days, and of the pregnant women who take acetaminophen, approximately 50% take it for headaches, 19% for pain, and only 8% for fever.[16] Acetaminophen crosses the placenta and reaches the fetal circulation and tissues.[57,58]

2. Normal Brain Development in Utero

The development of the brain and nervous system in utero is a complex and highly orchestrated process that involves the proliferation and migration of cells, the formation of neural circuits, and the establishment of synaptic connections. Here is a brief overview of the key stages of brain development in utero:

- Neural tube formation: The neural tube is the precursor to the brain and spinal cord. It forms during the first few weeks of gestation when the ectoderm (the outermost layer of cells) folds inward to form a groove, which then fuses to form a hollow tube. This process is called neurulation.

- Proliferation and migration of cells: Once the neural tube has formed, cells within the tube begin to rapidly divide and multiply. This process, called proliferation, creates the large numbers of neurons that will eventually make up the brain. As the cells divide, some of them migrate to their final positions within the brain, guided by chemical signals and physical cues.

- Formation of neural circuits: As the neurons migrate to their final positions, they begin to differentiate into specific types of cells and form connections with other neurons. This process, called synaptogenesis, creates the neural circuits that allow the brain to process information and perform its functions.
- Establishment of synaptic connections: As the brain continues to develop, the number and strength of synaptic connections between neurons increase. This process, called synaptic pruning, involves the elimination of weak or unnecessary connections and the strengthening of important ones.
- Myelination: Finally, during the third trimester of gestation and continuing into early childhood, a process called myelination occurs. Myelin is a fatty substance that surrounds and insulates the axons of neurons, allowing them to transmit signals more efficiently. Myelination is important for the development of complex cognitive and motor functions.

Overall, the development of the nervous system in utero is a complex and tightly regulated process that is critical for the formation of a properly functioning brain. The complex and tightly regulated nature of brain development in utero means that even minor or temporary disruptions to the process can have significant and long-lasting effects on the developing brain. (See section C.4. below.)

3. Deviations from Normal Brain Development: Neurodevelopmental Disorders

NDDs describe a category of conditions that result from deviations in normal brain development, resulting in a wide variety of symptoms that may include difficulties in areas such as learning, social skills, attention and behavior. While the causes of NDDs are often rooted in pregnancy, these disorders typically manifest themselves during childhood—when the functions of the child's brain can be fully assessed—and can impact an individual's ability to communicate, learn, and function throughout their lives.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[59], provides diagnostic criteria for several NDDs, including:

- Autism Spectrum Disorder (ASD): A NDD that affects communication and social interaction. Symptoms include deficits in social communication and interaction, restricted interests and repetitive behaviors, and sensory issues.

- Attention-Deficit/Hyperactivity Disorder (ADHD): A NDD that affects attention, hyperactivity, and impulsivity. Symptoms include inattention, hyperactivity, and impulsivity, and they can impact academic, social, and occupational functioning.
- Specific Learning Disorder (SLD): A NDD that affects academic skills such as reading, writing, or math. Symptoms include difficulties with reading accuracy, reading comprehension, written expression, and math calculations.
- Intellectual Disability (ID): A NDD that affects intellectual functioning and adaptive behavior. Symptoms include deficits in intellectual functioning (IQ) and adaptive behavior such as communication, daily living skills, and socialization.
- Communication Disorders: NDDs that affect speech, language, and communication. Examples include language disorder, speech sound disorder, and stuttering.
- Motor Disorders: NDDs that affect motor coordination, such as Developmental Coordination Disorder (DCD) or Tourette's disorder.

The DSM-5 provides detailed diagnostic criteria for each of these disorders, including the number and severity of symptoms required for diagnosis.

Importantly, different NDDs often have shared/overlapping symptomology as well as shared biological pathways or causes.[60] Various factors including the timing of the insult and individual susceptibilities are thought to determine which neurodevelopmental outcome(s) results from any given exposure or insult. Even with the same neurodevelopmental diagnosis, ASD for example, different individuals can present with very different symptoms and different levels of severity. At the same time, patients with different clinical diagnoses can have the same or similar overlapping symptoms. Therefore, in assessing the association between acetaminophen exposure in utero and neurodevelopmental disorders like ASD and ADHD, it is important to consider not just the clinical diagnoses but also the neurodevelopmental outcomes, including the symptoms.

a. Assessment of a Child with Symptoms of Neurodevelopmental Disorders

Assessing a child with symptoms of NDDs involves a comprehensive evaluation of the child's developmental history, behaviors, cognitive abilities, communication skills, and social interactions. The assessment process typically involves multiple stages, including:

1. Referral and intake: The child is referred for assessment, and the clinician collects information about the child's medical history, developmental milestones, and any previous assessments or interventions.
2. Interviews: The clinician conducts interviews with the child's parents, caregivers, and teachers to gather information about the child's behavior, communication skills, and social interactions.
3. Standardized assessments: The clinician administers standardized assessments to evaluate the child's cognitive abilities, language skills, social skills, and behavior.
4. Observation of the child’s behavior: The clinician observes the child's behavior and interactions with others in different settings, such as at home, at school, and in therapy sessions.
5. Screening for co-occurring conditions: The clinician may screen the child for co-occurring conditions such as ADHD, anxiety, or depression.
6. Diagnoses: Based on the assessment results, the clinician may make a diagnosis of a specific NDD, such as ASD, ADHD, or Specific Learning Disorder.

Overall, a thorough assessment of a child with neurodevelopmental symptoms requires a multidisciplinary approach involving clinicians, educators, and parents to provide a comprehensive understanding of the child's strengths and challenges and to develop an appropriate intervention plan.

The key steps involved in assessing a child with symptoms of NDDs are provided in *Assessment and Diagnosis of Neurodevelopmental Disorders in Young Children - A Practical Guide* by Neil Nicoll (Routledge Press, 2021) and typically include interviews, questionnaires, standardized tests and behavioral observations.[61]

i. Attention-Deficit/Hyperactivity Disorder

ADHD is the most frequently diagnosed and researched psychiatric disorder of childhood and it accounts for the majority of referrals to child and adolescent psychiatry services.[62] In the United States, 6 million (9.8%) children aged 3–17 years are estimated to live with a diagnosis of ADHD and/or ADHD-related symptoms, according to a national survey of parents,[63] with an estimated overall annual excess cost to society ranging between $143 to 266 billion annually[64]. Boys (13%) are more likely to be diagnosed with ADHD than girls (6%).[63] Many children diagnosed with ADHD also demonstrate symptoms consistent with other neurodevelopment disorders as well. As many as 64% of them have symptoms consistent

with another mental, emotional, or behavioral disorder, and 14% have symptomology consistent with a diagnosis of ASD.[63] Symptoms of ADHD persists into adulthood in many individuals, and the resulting burden in adults has been well described.

1) Symptoms and Clinical Features

Symptoms supporting a diagnosis of ADHD include a persistent pattern of inattention, hyperactivity, and impulsivity that can significantly impair a child's functioning and quality of life.[62,65]

In children, inattentive behaviors, such as frequent distraction, difficulty sustaining focus, and disorganization in managing materials or time, are common clinical manifestations that lead to a diagnosis of ADHD. On the other hand, excessive motor activity or restlessness in inappropriate contexts, fidgeting, talkativeness, and action without accompanying self-monitoring are behavioral aspects of hyperactivity and impulsivity that are often seen in individuals diagnosed with ADHD .[59]

The DSM-5 defines a unified ADHD symptom structure, which is further specified by presentations as predominantly inattentive, hyperactive/impulsive, or a combination of the two.[59] It is important to note that ADHD symptoms are not context-dependent and can manifest in multiple settings, such as home and school, resulting in impairments in academic or interpersonal environments. These impairments can lead to learning difficulties, social rejection by peers and family, or elevated interpersonal conflict.[59,62]

Moreover, to support a diagnosis of ADHD, the onset of symptoms must occur during the child's developmental period, which is defined as prior to age 12 years in the case of ADHD, expanded from prior definitions (*e.g.*, before age 7 years in DSM-IV).[65]

As indicated below, the diagnosis of ADHD in children is based on the presence of certain neurodevelopmental symptoms and involves a comprehensive evaluation that takes into account the child's behavior at home, school, and in other settings. The evaluation may include input from parents, teachers, and other caregivers, as well as observations and testing by a medical professional.

2) Prevalence and Epidemiology

Attention-Deficit/Hyperactivity Disorder (ADHD) is now the most commonly diagnosed pediatric behavioral disorder, with prevalence rates ranging between 5% and 10% in the general population.[66]

Although rates of ADHD diagnoses decrease in adulthood, with estimates ranging from 2.5% to 5.0%[67], prevalence rates appear to differ by age and sex. Male : female ratios range from 2 : 1 to 4 : 1, but there is debate over the potential influence of referral bias, as girls may be less likely to be referred for ADHD evaluation.[68] Moreover, evidence indicates that girls diagnosed with ADHD are more likely than boys to have the inattentive presentation of the disorder. Studies focusing on girls with ADHD suggest that affected girls may carry an increased disease burden, particularly during adolescence, when they are more likely to experience issues related to self-harm or emotional dyscontrol.[69]

3) Causes and Risk Factors

The complex cognitive and behavioral domains affected by the development of ADHD-related symptomology involve high-level cognitive functions that rely on multiple executive and control processes. These multidimensional processes are vulnerable to disruption during neurodevelopment. Recent genetic data consortia have identified several candidate genes implicated in the development of ADHD-related symptomology. However, the limited odds ratios associated with single-gene polymorphisms support the multifactorial nature of underlying the development of ADHD-related symptoms. “The heritability that cannot be explained by main effects of rare or common variants is likely due to gene-gene interactions, gene-environment interactions or gene-environmental correlations.” “The convincing evidence for genes as risk factors for ADHD does not exclude the environment as a source of etiology. The fact that twin estimates of heritability are less than 100% asserts quite strongly that environmental factors must be involved. ADHD’s heritability is high, and that estimate encompasses gene by environment interaction. Thus, it is possible that such interaction will account for much of ADHD’s etiology. Environmental risk factors likely work through epigenetic mechanisms, which have barely been studied in ADHD.”[70]

Several physiological and environmental risk factors have been linked to ADHD, including low birth weight, infant malnutrition, unhealthy maternal diet, maternal smoking during pregnancy, child abuse, exposure to teratogens or environmental toxins, and sensory, sleep, and metabolic impairments, among others.[71]

4) Diagnostic Evaluation[62]

ADHD diagnoses will typically be based on a thorough clinical assessment, entailing history of deficits in both inattentive and hyperactive—impulsive domains. History-taking focuses on determining the age at onset of symptom presentation and placing symptoms within the context of a developmental and

sociocultural framework. Family and medical histories are needed to identify potential etiologies and to rule out other potential diagnostic classifications. Collateral information is critical, often due to varying levels of perception of symptom burden based on reporter source and diagnostic criteria requiring presence of symptoms in multiple settings. Therefore, observer reports from family members, teachers, coworkers, or roommates are essential. Despite variability in symptom scale reports based on reporter sources, standardized assessments are also important sources of information. Historical records from school settings and parental observations are particularly useful in establishing a diagnosis in adults presenting for evaluation. Neuropsychological testing may be helpful but is not required for a diagnosis of ADHD. In fact, despite strong evidence that neuropsychological domains are disproportionately affected in ADHD relative to typical development, the specific cognitive domains affected are heterogeneous, and identification of clear neuropsychological phenotypes has remained elusive, although there continues to be progress in this area.

To account for a stable core diagnostic structure in ADHD, which may vary over time in phenomenology, DSM-5 provides three classes of specifiers to characterize: 1) the symptom presentation in the previous 6 months, defined as predominantly inattentive, hyperactive/impulsive, or combined; 2) the degree of severity as mild, moderate, or severe based on level of functional impairment; and 3) whether symptoms that had previously met full criteria are in partial remission at the time of evaluation.

In cases in which full criteria for ADHD are not met, DSM-5 allows assignment of the diagnostic category "other specified attention-deficit/hyperactivity disorder" to indicate the presence of symptoms characteristic of ADHD that cause clinically significant distress or impairment but do not meet the full criteria for a diagnosis of ADHD or another NDD. Therefore, a diagnosis of "other specified attention-deficit/hyperactivity disorder," followed by "with insufficient symptoms" in the relevant domain (*e.g.*, inattention, hyperactivity/impulsivity), may be assigned. In presentations where criteria are not met but significant impairment related to ADHD-related symptoms is present, a diagnosis of unspecified attention-deficit/hyperactivity disorder may be assigned without identifying the domain with insufficient symptoms.

ii. Autism Spectrum Disorder (ASD)

1) Symptoms and Clinical Features

ASD is a type of NDD defined and described with its own diagnostic criteria set forth in the DSM-5 that typically becomes symptomatic in early childhood and is diagnosed based on symptomology

characterized by deficits in social interaction and communication, stereotypical behaviors, insistence on sameness, restricted interests, and abnormal sensory processing.[59]

ASD describes a highly diverse NDD with a wide range of clinical and symptom-related presentations. The DSM-5 outlines the diagnostic criteria for ASD, which requires the presence of all three social communication criteria and at least two of the four additional criteria, with onset of symptoms in the early developmental period.[59]

The three social communication criteria for a diagnosis of ASD are deficits in social-emotional reciprocity, nonverbal communicative behaviors, and developing, maintaining, and understanding relationships.[59] The four additional criteria for a diagnosis of ASD are stereotyped or repetitive motor movements, cognitive inflexibility or ritualized patterns of verbal or nonverbal behavior, highly restricted, fixated interests, and hyperreactivity or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.

To better understand the interindividual differences in children diagnosed with ASD, DSM-5 specifiers have been developed. These include severity, the presence or absence of intellectual impairment, language impairment, association with a known medical or genetic condition, association with another neurodevelopmental, mental, or behavioral disorder, and the presence of catatonia.[59]

2) Prevalence and Epidemiology

Over the past three decades, the prevalence of ASD diagnoses has steadily increased.[72–74] In the mid-1970s, the ASD prevalence was estimated at 5 cases per 10,000 children in the US.[62] Reported prevalence has increased substantially since that time, with the most recent estimated prevalence being 27.6 per 1,000 (1 in 36) children at age 8 years—*i.e.*, 276 cases per 10,000, a more than 50-fold increase—and with pronounced sex differences (*i.e.*, a male-to-female ratio of 3.8 to 1).[74] A pattern of increasing ASD prevalence over time has been found in all countries in which multiple studies have been conducted.[75] Clearly, some of the increase is attributable to improved detection, increased awareness, and use of broader diagnostic criteria.[76] However, these factors do not appear to fully explain the dramatic rise in ASD. The increase in ASD prevalence appears to apply to all socioeconomic levels, races, and ethnicities.[62]

ASD can be diagnosed in comorbidity with ADHD according to DSM-5. ADHD-related symptomology and/or diagnosis is present in 33%–37% of ASD cases, with the comorbid symptomology being

characterized by greater deficits in executive functions and in emotional self-regulation compared to cases diagnosed as ASD alone.[77]

3) Causes and risk factors

The etiology of ASD is generally accepted to be multifactorial, including both genetic and environmental causes. There are two recognized classifications of genetic factors that play a causal role in ASD, syndromic and non-syndromic.

Syndromic genetic causes, such as chromosomal abnormalities and de novo copy number variations, account for about 10% to 20% of ASD cases. Fragile X syndrome is an example of syndromic genetic cause and is the most common monogenic cause of ASD, with about 28% of males and 11% of females with the syndrome that also meet the DSM-5 criteria for ASD.[78] Other genetic syndromes highly associated with ASD include Rett syndrome (61%), Cohen syndrome (54%), Cornelia de Lange syndrome (43%), tuberous sclerosis complex (36%), Angelman syndrome (34%), and neurofibromatosis type 1 (18%).[79]

Non-syndromic genetic factors are thought to play a contributing role in the development of ASD. AutDB, a curated database for autism research, has associated more than 800 genes with ASD, with over 70 risk loci strongly linked to the disorder,[80] however, no single genetic etiology accounts for more than 0.2% of cases among individuals with non-syndromic ASD. In the multifactorial model of ASD, genetic factors combine with environmental exposures to cause ASD. Research suggests that exposure to certain environmental factors during critical periods of brain development can interact with genetic predispositions or susceptibilities and even modify gene expression leading to abnormal neurodevelopment in the fetal brain.[81] For example, studies have shown that maternal infection or inflammation during pregnancy can alter gene expression in the developing fetal brain and increase the risk of ASD.[82] Additionally, exposure to certain chemicals, such as pesticides or prescription medications, during pregnancy may also increase the risk of ASD in genetically susceptible individuals.[83]

4) Diagnostic Evaluation

Various professional organizations have published guidelines for the assessment of ASD, including a practice parameter by the American Academy of Child and Adolescent Psychiatry.[84] Generally, there are two levels of evaluation: Level 1 screening involves routine developmental surveillance by primary care physicians for young children, and Level 2 evaluation involves a more comprehensive diagnostic assessment by experienced clinicians, such as child and adolescent psychiatrists, pediatric neurologists,

developmental and behavioral pediatricians, child psychologists, speech and language pathologists, for children with significant ASD symptomatology identified through screening. The Level 2 assessment usually includes a review of presenting symptoms; a psychiatric review of systems; a psychiatric and behavioral history; a detailed developmental, school, medical, and social history obtained from parents and care providers; a review of available records, such as school reports and neuropsychological testing; and direct observation of and interaction with the child.

Although standardized instruments are not required to establish a diagnosis of ASD, many clinics use them in routine assessments. The gold standard diagnostic tool for direct assessment of symptoms is the Autism Diagnostic Observation Schedule, a 40-minute semi-structured interaction designed for multiple modules that are developmentally appropriate from infancy through adulthood and across the range of functioning levels. The Autism Diagnostic Interview-Revised (ADI-R) is used to establish the developmental history required for ASD diagnosis in some clinical and most research settings. It is a semi-structured comprehensive interview for parents or caregivers of children and adults being diagnostically assessed for ASD.[62]

Differential diagnosis and clinical judgment play an important role in the determination of whether presenting neurodevelopmental symptoms support a diagnosis of ASD. For example, poor eye contact and low social initiative are common in individuals with ASD, and also in individuals diagnosed with depression, anxiety, schizoid personality disorder, or avoidant personality disorder. However, individuals meeting the diagnostic criteria for ASD often have abnormal psychomotor function and inattention, which are absent in the diagnostic criteria for schizoid and avoidant personality disorders. Obsessive-compulsive disorder (OCD) is another condition commonly included in the differential diagnosis of ASD. Although rituals and compulsions can be part of the diagnostic symptomology for both ASD and OCD, there are subtle differences in the presentation of these symptoms that allow clinicians to properly diagnose the patient. For example, the compulsions associated with ASD are typically related to sensory-seeking behaviors or restricted interests, whereas the compulsions associated with OCD are related to contamination fears, superstitions, and repeated doubts.[62]

4. Pregnancy as Window of Susceptibility for Adverse Effects on the Developing Brain

Pregnancy is a "critical period" when the developing brain is highly susceptible to the effects of toxic exposures. Embryonic and fetal life is recognized as being a state of sequential physiological and developmental shifts.[85] This timed cascade of biological events means that the embryo and fetus are

highly vulnerable to even subtle environmental insults, as cell and tissue differentiation is most active at this life stage. The rapid growth of the brain during the second trimester of fetal development is followed by neuronal migration, differentiation, proliferation, and pruning throughout early childhood.[41] Growing cells are more vulnerable to exposures, and the brain forms over a longer period than do other organs.[41,86] Finally, the brain is composed of many different types of neurons, as well as other cells such as oligodendrocytes, astrocytes, and microglia, each type having a distinct growth phase and potentially a different toxicity and susceptibility profile.

Some of the earliest reports on pregnancy as a window of high susceptibility came from David Barker's research team, which conducted a series of seminal studies on fetal nutritional environment and subsequent adult cardiometabolic health.[87–89] Increasingly, the observation that early life nutritional famine was a strong predictor of later life hypertension, obesity and even neurobehavioral disorders such as schizophrenia,[90,91] has become an accepted biological tenet. Research on the fetal chemical and social environment has found many parallel effects to the Barker hypothesis that solidified the concept that pregnancy is a "window of susceptibility" or "critical window."

Today, the vulnerability of the developing brain during pregnancy to the effects of chemicals is widely accepted as a biological fact. The embryonic and fetal stages are times of rapid and sequential physiological and developmental changes, making the developing brain particularly susceptible to insults. The developing brain is especially vulnerable to exposures because of the incomplete development of the blood-brain barrier and the ongoing growth, differentiation, and pruning of neurons throughout early childhood. The recognized potential mechanisms that support biologic plausibility include (1) excess production of toxic metabolite NAPQI; (2) oxidative stress, inflammation, immune reaction; (3) reduced production of prostaglandin; (4) endocannabinoid dysfunction; (5) alterations in BDNF production and distribution; (6) endocrine disruption; and (7) epigenetic changes.[7]

E. MECHANISMS OF ACTION LINKING PRENATAL ACETAMINOPHEN TO ADVERSE EFFECTS ON CHILD NEURODEVELOPMENT

To evaluate whether there is a causal relationship between prenatal acetaminophen exposure and neurodevelopmental outcomes in children, it is helpful to understand the biologic plausibility linking in utero exposure with altered fetal brain development.

1. Acetaminophen Crosses the Placenta Unchanged and Can Directly Impact the Fetal Brain.

The placenta is an essential organ that develops during pregnancy and provides a crucial link between the mother and the developing fetus. One of its primary functions is to act as a barrier between the maternal and fetal circulations, preventing the direct exchange of substances between the two. This barrier protects the developing fetus from potentially harmful substances that may be present in the mother's bloodstream, including some drugs, toxins, and infectious agents.[92]

Acetaminophen, however, has been long known to freely cross the placental barrier,[57,58] meaning it easily and rapidly enters the fetal bloodstream and within less than an hour of maternal ingestion, acetaminophen reaches a level in the fetal circulation similar to that in the maternal circulation.[93,94] Since both the fetal brain and the placenta have been shown to have measurable levels of the metabolizing enzyme, CYP2Ee1[47,95] it is of great concern that the acetaminophen that reaches the fetal circulation and the fetal brain can be metabolized to the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI.) NAPQI is known to be toxic to hepatocytes and to be the cause of acetaminophen liver toxicity with its associated morbidity and mortality.[43,93] Acetaminophen is also toxic to human cells through the generation of oxidative stress and by causing the depletion of glutathione.[43]

2. Acetaminophen and Increased Oxidative Stress

The fetal developing brain is particularly vulnerable to toxin-induced injury, including oxidative stress, even at low levels of exposure. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's capacity to detoxify them using antioxidants. Prenatal exposure to acetaminophen has been linked to increased oxidative stress,[96] which can adversely affect the developing brain in utero.

Acetaminophen can increase oxidative stress both through the production of NAPQI and through depletion of the body's antioxidant stores, including glutathione, which plays a crucial role in reducing oxidative stress.[97]

The developing brain is highly susceptible to the effects of oxidative stress because it is rapidly growing and maturing and requires enormous energy metabolism. Oxidative stress can cause cellular damage, leading to impairment of neuronal and glial cell function, disrupted neural connection formation, and abnormal brain function.[98] Indeed, animal studies have found that prenatal exposure to acetaminophen

results in an increase in oxidative stress markers in the fetal brain and associated neurodevelopmental deficits. Evidence supporting acetaminophen's ability to produce oxidative stress in the fetal brain and the ability of brain cells to metabolize acetaminophen to produce the toxic metabolite NAPQI provide evidence of biologic plausibility for acetaminophen's neurodevelopmental effects on the fetal brain.

3. Acetaminophen and Alterations of the Prostaglandin System

One of acetaminophen's primary actions is its effect on the production of prostaglandins, which is a potential mechanism underlying its action to reduce fever. The antipyretic properties of acetaminophen are attributed to its ability to inhibit cyclooxygenase enzymes in the brain that synthesize prostaglandins.[99] Prostaglandins mediate the generation of fever but also are involved with prenatal neuronal development, including the development of synaptic plasticity in the developing brain.[100,101] Prostaglandin E2 is involved in the normal development of the brain and is essential in regulating the development of the cerebellum and the preoptic area of the brain.[102] Abnormalities in the prostaglandin E2 signaling pathway due to genetic defects or exposure to environmental factors during critical periods of brain development have been associated with the etiology of NDDs, including ASD.[100,103,104] Overwhelming evidence shows that chemicals that disrupt the levels of prostaglandin E2, including drugs such as misoprostol (prostaglandin E analogue),[103] air pollutants, and chemicals found in food and personal care products like cosmetics, are independently linked to ASD.[101] Recent evidence also indicates that the prostaglandin system is also altered in individuals diagnosed with ADHD. Acetaminophen's modulation of the prostaglandin pathways during a sensitive neurodevelopmental window such as pregnancy provides a potential, and biologically plausible, mechanism of injury to explain the association between in utero exposure to acetaminophen and neurodevelopmental outcomes, including ASD and ADHD.

4. Acetaminophen and Alterations of the Endocannabinoid System

Studies show that prenatal alterations of the endocannabinoid system are one of the potential, and biologically plausible, mechanisms through which prenatal acetaminophen can adversely impact the developing brain.[105] It is thought that the analgesic effect of acetaminophen acts through the endocannabinoid system.[106] The endocannabinoid system is a complex network of lipid signaling pathways that have an important role in the developing nervous system including the developing brain at each stage of its development.[7] Alterations of the endocannabinoid system have been found in both the brain and the immune system of humans with ASD.[107,108] Studies in mice have demonstrated the

emergence of ASD-like behaviors following diverse genetic or pharmacological manipulations targeting the endocannabinoid system.[109]

Cannabinoid receptors (CB1 and CB2) and their ligands have been the focus of extensive research as they are increasingly associated with pathologic conditions. CB1 receptors are highly expressed in the central nervous system (CNS) in areas such as the basal ganglia, hippocampus, and cortex, as well as in the peripheral nervous system (PNS). CB1 receptors are involved in the modulation of postsynaptic neurotransmitter release by pairing with voltage-gated calcium channels in the presynaptic neurons.[110] They are also required for normal axonal growth and synaptic plasticity.[111] Maternal cannabis consumption during pregnancy can activate CB1 receptors and lead to behavioral deficits in children due to their role in embryonal neuronal connectivity.[112] In contrast, CB2 receptors are mostly restricted to immune tissues and cells[113] and are not significantly influenced by acetaminophen.

Acetaminophen effects on the endocannabinoid and prostaglandin pathways alone or in combination are biologically plausible mechanisms by which in utero acetaminophen exposure may cause neurodevelopmental injury to a fetus. [100,114–119]

5. Acetaminophen and Brain-Derived Neurotrophic Factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is a protein that plays an important role in the growth, survival, and maintenance of neurons (nerve cells) in the brain and nervous system.[120] BDNF is a member of the neurotrophin family of growth factors, which are small proteins that support the development and function of the nervous system. BDNF is produced in the brain and released by neurons in response to activity and other stimuli.[121] It binds to specific receptors on the surface of neurons, triggering a signaling cascade that promotes neuron growth, differentiation, and survival.[122,123] Disruption of BDNF and its downstream signals has been observed in patients diagnosed with NDDs, including ADHD and ASD.[124,125]

Acetaminophen administration in mice during neonatal brain development was shown to affect BDNF in the neonatal brain and subsequently impair cognitive function and analgesic and anxiolytic response in adult male mice.[126] BDNF has a distinct pattern during the brain growth spurt. It promotes neuronal survival and also regulates cell migration, axonal and dendritic outgrowth, and formation and function of synapses. Therefore, acetaminophen-induced changes BDNF alterations in the developing brain in utero provide a potential and plausible mechanism to explain neurodevelopmental outcomes including ASD and ADHD as well as other behavioral and cognitive alterations diagnosed during childhood.

6. Acetaminophen and Endocrine Effects

The endocrine system is a complex network of glands and organs that produce and secrete hormones into the bloodstream. These hormones act as chemical messengers that regulate many physiological processes in the body, including growth, metabolism, and reproductive functions. During prenatal development, the endocrine system plays a crucial role in the development of the brain, as it regulates the production and activity of hormones that are essential for healthy neurological development. Disruptions to the endocrine system, such as exposure to endocrine-disrupting chemicals, can interfere with the activity of these hormones and potentially lead to permanent structural and functional alterations in the developing brain.

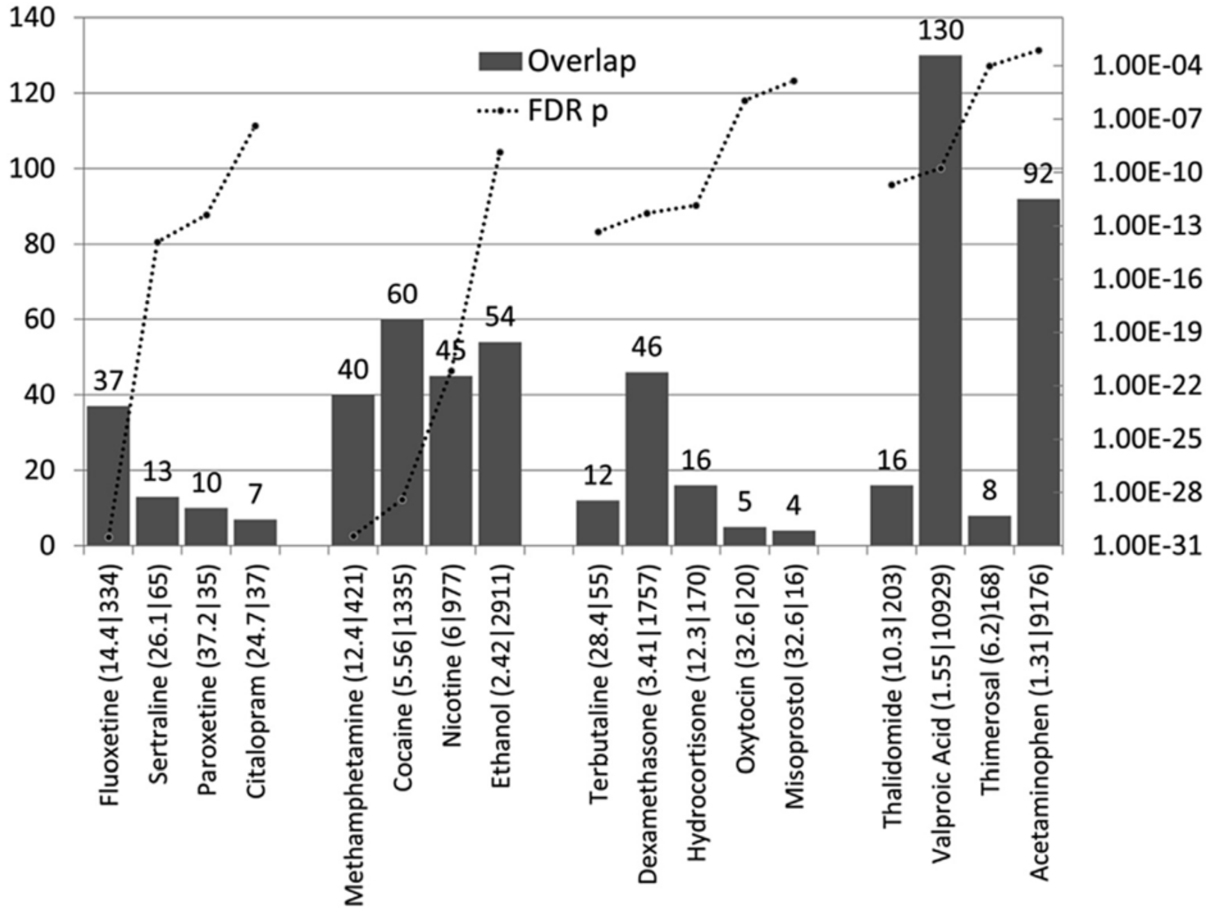
Studies have found that acetaminophen is an endocrine disruptor that directly perturbs hormone-dependent processes, affects neurodevelopment and reproductive disorders, and might alter steroidogenesis in the placenta and induce placental damage. Indeed, acetaminophen has many of the key characteristics for hazard identification of an endocrine-disrupting chemical: in vivo, in vitro and ex vivo studies have shown that acetaminophen directly perturbs hormone-dependent processes, including inhibition of androgen production and increased estrogen production, disruption of steroidogenesis, and depletion of sulfated sex hormones.[114,127,128] Independently of acetaminophen, these processes have been implicated as mechanisms related to the development of NDDs,[102] including ASD and ADHD.

7. Acetaminophen and Epigenetic Effects

The epigenome refers to a set of chemical modifications that can affect how genes are expressed, or "turned on" or "off," without changing the underlying DNA sequence.[129] One example of an epigenetic modification is DNA methylation, which involves the addition of a chemical group to a specific part of the DNA molecule. This modification can act like a switch to turn off a gene, preventing it from being expressed. During prenatal development, the epigenome undergoes a series of dynamic changes that regulate gene expression and cell differentiation.[129] Alterations in the epigenome can result in abnormal gene expression, leading to various NDDs, including ADHD, and ASD.[130]

Epigenetic modifications, such as DNA methylation, play crucial roles in regulating gene expression during brain development.[131,132] For example, genes involved in neurogenesis, neuronal differentiation, and synaptic plasticity are epigenetically regulated.[132] Disruption of epigenetic marks can lead to alterations in gene expression, which can affect various aspects of brain development and function, such as neuronal migration, synaptogenesis, and myelination.[5] Moreover, alterations in the epigenome can

lead to changes in neural networks, which are critical for normal brain function.[133] Interestingly, as shown in the figure below, Carter and Blizzard found that acetaminophen was one of the medications the produced the strongest alterations on the expression of ASD genes, with a combined 92 genes whose expression was modified by acetaminophen,[134] second only to Valproic Acid which is known to cause ASD and ADHD[135].



Prenatal acetaminophen has been associated with DNA methylation changes in fetal tissues and the placenta. Eslamimehr et al. (2022), identified DNA methylation changes in 10 genes that were associated with prenatal use of acetaminophen.[136] Addo et al. (2019), identified changes in methylation in placentas at 42 loci that were associated with prenatal acetaminophen use.[116] Some of the loci identified are vital to neurodevelopment. For instance, EAF1 is an RNA polymerase transcription elongation factor and is highly expressed in several endocrine organs including the uterus, testis, and the placenta.[137] Among its many functions, EAF1 represses patterning of neuroectoderm and mesoderm

during embryogenesis by downregulating the Wnt/β-catenin signaling pathway, a pathway that is essential for neurodevelopment.[138] Strong support for the effects of prenatal acetaminophen on the child's epigenome also comes from a study in a subpopulation of the MoBa cohort. This study analyzed cord blood samples and found significant differences in DNA methylation in genes involved in oxidative stress and neural transmission pathways in children diagnosed with ADHD who were exposed long term to acetaminophen in pregnancy compared to controls.[139]

Gervin et al. (2017),[139] investigated the association between prenatal exposure to paracetamol and DNA methylation in children diagnosed with attention-deficit/hyperactivity disorder (ADHD). As the authors stated, "this study identified altered DNA methylation differences at genes involved in oxidative stress, neural transmission, and olfactory sensory pathways associated with long-term exposure to paracetamol during pregnancy in children diagnosed with ADHD." Further the authors explained, "these results suggest that in individuals susceptible to ADHD, prenatal long-term exposure to paracetamol is associated with DNA methylation changes. That is, individuals susceptible to ADHD respond differently compared to controls to long term paracetamol exposure during development." The study supports the epidemiological evidence of increased risk of developing ADHD with long term acetaminophen exposure and provides evidence that prenatal long-term exposure to paracetamol is associated with DNA methylation differences that may lead to ADHD.

Spildrejorde et al. (2022),[140] investigated the effects of paracetamol on early human brain development using a multi-omics approach. Human embryonic stem cells were exposed to paracetamol concentrations corresponding to maternal therapeutic doses, and the results showed paracetamol-induced chromatin-opening changes linked to gene expression. The differentially methylated and/or expressed genes were involved in signaling, neurotransmission, and cell fate-determination trajectories. The study further suggests that paracetamol may play a causal role in impaired neurodevelopment, with implications for prenatal paracetamol exposure and its potential impact on brain development.

In summary, alterations in the epigenome during prenatal development can have significant effects on brain development and function, leading to various neurodevelopmental deficits. Strong evidence suggests that prenatal acetaminophen determines epigenetic changes, particularly in DNA methylation, which provide a potential and plausible mechanism of injury resulting from in utero exposure to acetaminophen leading to NDDs including ASD and ADHD.

8. Summary of the Available Evidence on the Mechanisms of Action

The available evidence on the mechanisms of action provides support to the causal link between prenatal acetaminophen exposure and adverse effects on the developing brain. Acetaminophen crosses the blood-brain barrier (BBB) easily and within less than an hour of exposure acetaminophen levels in fetal blood have been shown to match those found in the maternal blood.[93,94] Both the fetal brain and the placenta have been shown to have measurable levels of CYP2E1 which would metabolize acetaminophen producing the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI is toxic to human cells, depletes glutathione and increases oxidative stress. Acetaminophen also s reduces the production of prostaglandin, alters the endocannabinoid systems and disrupts the endocrine system, all of which play a crucial role during brain development. Acetaminophen alters brain cell growth by affecting brain-derived neurotrophic factor (BDNF). Finally, there is evidence that acetaminophen can reprogram the fetal epigenome, a molecular change that can have long lasting consequences. Together, these mechanisms identify several plausible biologic causal pathways by which prenatal acetaminophen exposure could lead to NDDs, including ADHD, and ASD.

F. THE SCIENCE OF EPIDEMIOLOGY

Epidemiology is a scientific field that investigates diseases in human populations. Its purpose is to identify the causes of the diseases and to find approaches to prevent their occurrence. By observing patterns of disease occurrence, epidemiologists aim to describe and explain the distribution of health and disease within human populations.

When available, the double-blind randomized controlled trial (RCT) provides particularly powerful evidence of causation. By using randomization, researchers are able to create two groups of individuals presumed to be identical (as a group) in all relevant respects. After randomizing which individuals receive the treatment, and which receive the control, researchers are then able to compare outcomes. If one group shows more (or less) of an outcome than the other, that is strong evidence of causation, since no pre-existing feature of the two groups can explain the difference. RCTs can be used when the substance in question is not thought to be harmful. For instance, vitamin supplements have been tested in large-scale clinical trials to determine their impact on the risk of several diseases—including cancer and cardiovascular disease—as the expectation was that they could be beneficial and unlikely to pose risks for study participants.

Though desirable, it is not always possible to use an RCT to determine causation. For example, if a certain substance is thought to be potentially harmful, it is unethical to give that substance to one randomized group of patients.[141] There are several situations where an RCT may be considered unfeasible and/or unethical due to potential harm, including:

1. When the intervention being tested has known serious adverse effects, particularly if there are other effective treatments available.
2. When the risks associated with the intervention are not fully understood such that it may be difficult to determine whether the potential benefits of the intervention outweigh the risks.
3. When the study population is particularly vulnerable, such as children, elderly individuals, or individuals with mental illness.
4. When the risks associated with the intervention are greater than the potential benefits.

That is the situation here. Randomized clinical trials do not allow us to answer questions regarding drug safety in pregnancy, because it would be unethical to randomly give a pregnant woman a substance that might harm the developing fetus.[141] This is true for drug safety studies during pregnancy generally, and more specifically, Castro et al. (2022), stated that it would be unethical to use randomized clinical trials to assess the possible adverse effects of acetaminophen on the developing fetus.[142]

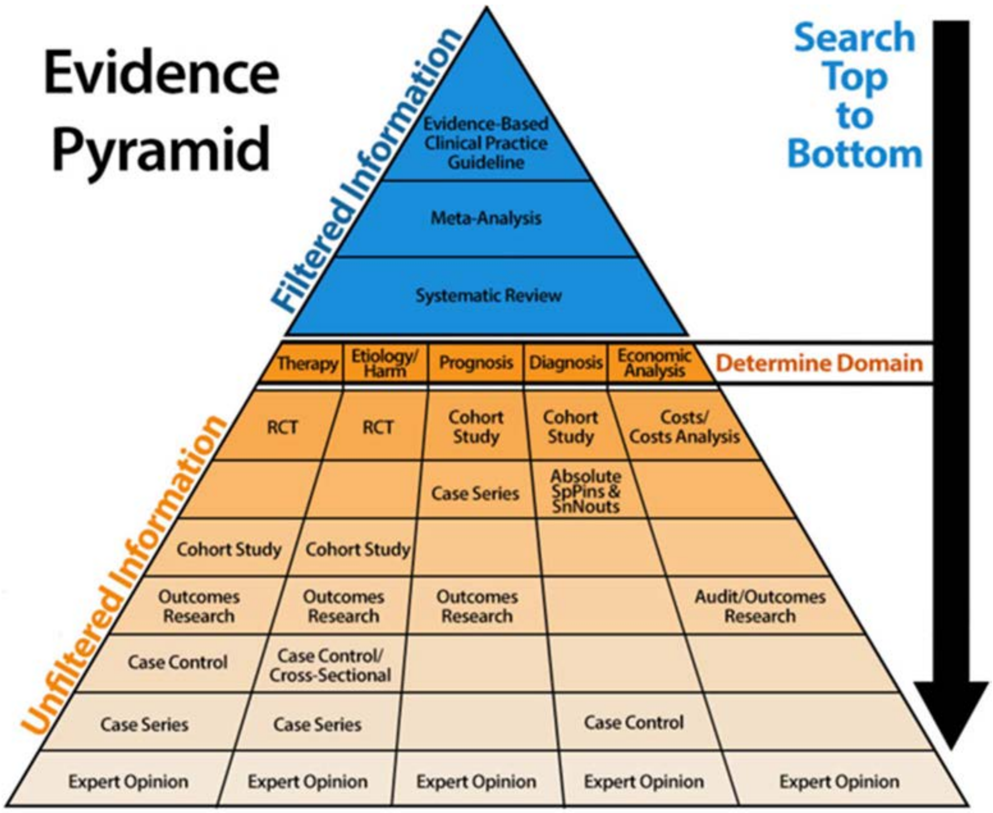
When RCTs cannot be employed, epidemiologists typically turn to observational studies. These studies are done by comparing observations made at the individual level within populations. These studies can identify differences in the incidence rate of a certain disease in populations exposed (or not exposed) to a certain substance. To the extent that the studies can control for potential confounding factors—differences between the exposed and unexposed groups that might themselves cause the disease—they also can provide powerful evidence of causation.

Especially in situations when RCTs cannot be used, observational studies have contributed significantly to our understanding of public health. They have shown that excessive alcohol consumption increases the risk of liver failure and other diseases,[143] that obesity increases the risk of diabetes,[144] and that smoking increases the risk of lung cancer[145] and cardiovascular disease.[146] None of these links could have been demonstrated via a RCT—it would be unethical to randomly force people to drink alcohol, to become obese, or to smoke simply to determine whether those exposures caused the disease of interest. But via repeated observations, numerous controls for confounders, and statistical techniques,

researchers have nevertheless been able to use observational studies to demonstrate that these associations are likely causal.

Observational studies have also been commonly used to evaluate the effects of prenatal exposures on neurodevelopment. For instance, observational studies identified the link between prenatal use of valproate—a commonly used medication used to prevent seizures in individuals with epilepsy—and ASD and other neurodevelopmental deficits.[147] This link is now warned about in the valproate label itself.[135] Observational studies also identified the adverse effects of exposure to lead during pregnancy on the developing brain, which resulted in the ban on leaded gasoline.[148] Observational studies have been the basis of many other policy and industry decisions that reflected the learning from epidemiological studies related to the risk of several diseases, such as the impact of radium exposure[149] on bone health, blood abnormalities, and cancers, and secondhand smoke on the risk of lung cancer in nonsmokers.[150]

It is helpful to see the quality and quantity of evidence that may be available when assessing a causal relationship. The highest quality evidence is at the top of the pyramid, and as one goes down the pyramid, the amount of evidence will increase as the quality simultaneously decreases. In addition to original studies, epidemiologist look to what is referred to as “filtered information”—systematic reviews, meta-analyses, and evidence-based clinical practice guidelines—that undertake reviews of multiple original studies. Those three categories sit at the top of the pyramid as the highest quality of evidence.[151,152]



The association between prenatal acetaminophen use and NDDs has been studied in two types of epidemiological studies: case-control and cohort. Therefore, the following description of epidemiological methodology focuses on these types of studies. Before describing them, it is necessary to define some terminology.

1. Terminology in Epidemiological Studies

a. Risk

The term risk refers to the likelihood of a disease occurring. In epidemiological research, the risk is often expressed in relative terms, comparing the risk of disease development in one group to that of another. In the field of prenatal epidemiology, risk primarily refers to the risk associated with an exposure during pregnancy.

b. Risk Factor

A risk factor is any attribute, characteristic, or exposure that increases an individual's chances of developing a disease or injury. Risk factors can be inherent, such as age, sex, and genetics; lifestyle-related, such as diet, physical activity, or smoking; health-related, such as menstrual factors, reproductive history, or history of infectious diseases; toxic exposures, such as minerals, metals, chemicals, or radiation; or medical, such as use of particular medications.

c. Exposures

In epidemiological research, an exposure is a factor or condition that may increase or decrease the risk of disease (or have no effect). This report focuses on the use of prenatal acetaminophen as the exposure under investigation and analyzes whether it is causally associated with NDDs including ADHD and ASD.

d. Association

In epidemiology, association refers to a statistical relationship between an exposure (*e.g.*, a risk factor) and an outcome (*e.g.*, a disease or health condition) observed in a population. A positive association means that exposed populations have a higher probability of experiencing the outcome of interest than unexposed populations. For example, a study may find that those who smoke cigarettes have a higher risk of developing lung cancer. On the other hand, a negative association means that exposed populations have a lower probability of experiencing the outcome of interest than unexposed populations. For example, a study may find that those who engage in physical activity have a lower risk of developing heart disease. An association does not necessarily imply causation, but it suggests that there is a relationship between the exposure and the outcome that requires an explanation. Epidemiologists use various study designs and statistical methods to determine whether an association is causal or not, as described in greater detail in Part D.5 of this report.

e. Etiology

The etiology of a disease or condition refers to its cause(s) or origin. Diseases in an individual, particularly NDDs, may have more than one cause.

f. Multi-Factorial Etiology

The etiology, or cause, of most NDDs is multifactorial, meaning that there are many factors that contribute to the development of these disorders. Some of the most important factors that have been identified include genetic predisposition, environmental factors, maternal alcohol and substance abuse, smoking, toxic chemicals, and medications. Epidemiologists use a variety of methods to identify the contribution of each risk factor to a disease with multifactorial origin, including covariate-adjustment, stratification, and interactions.[153]

g. Relative Risk, Odds Ratio, and Hazard Ratio.

Relative risk, odds ratio, and hazard ratio are three common measures used in epidemiology and statistics to describe the strength of association between a risk factor and a disease outcome.

Relative risk (RR) is the ratio of the risk of disease in the exposed group (*i.e.*, those with the risk factor) compared to the risk of disease in the unexposed group (*i.e.*, those without the risk factor). An RR greater than 1 indicates that the risk factor is associated with an increase prevalence in populations with that risk factor. A RR less than 1 indicates that the risk factor is associated with a decreased prevalence of the disease in populations with the risk factor. For instance, an RR of 1.3 indicates that populations with the risk factor being studied have a 30% higher risk of developing the disease outcome compared to those without the risk factor. As an example, if we were looking at the risk of developing a disease in smokers versus non-smokers, and the RR were 1.3, then the risk of developing the disease would be 1.3 times higher in smokers compared to non-smokers. An RR of 0.7 indicates that populations with the risk factor being studied have a 30% lower risk of developing the disease outcome compared to those without the risk factor.

Odds ratio (OR) is another measure used to estimate the strength of association between a risk factor and a disease outcome. OR is calculated by dividing the odds of exposure in the cases (*i.e.*, those with the disease) by the odds of exposure in the controls (*i.e.*, those without the disease). OR is commonly used in case-control studies when the incidence of the disease is low. The meaning and interpretation of the OR is similar to that of the RR—and OR of 1.3 means that the odds of developing the disease among individuals with the risk factor being studied are 30% higher compared to those without the risk factor.

Hazard ratio is a statistical measure that quantifies the relative risk of an event or outcome occurring in one group compared to another group over time. It is commonly used in survival analysis, where researchers investigate the time it takes for an event of interest to occur, such as death or disease onset, and assess the differences between groups. A hazard ratio of 1 indicates that there is no difference in the risk of the event or outcome occurring between the two groups. A hazard ratio greater than 1 indicates that the risk of the event or outcome is higher in the first group than the second group, while a hazard ratio less than 1 indicates that the risk is lower in the first group than the second group. For example, if we were studying the effect of a particular treatment on the survival of patients with diabetes and found that the hazard ratio for the treatment group compared to the control group was 1.3, this would mean that the risk of death for the treatment group is 1.3 times higher than the control group. In other words, the treatment group has a 30% higher risk of death than the control group.

h. Statistical Analyses

Epidemiologists utilize various statistical analyses to evaluate the magnitude and significance of the associations among variables in datasets. Relative risk, odds ratio, and hazard ratio are the most commonly used in observational studies. To estimate the precision and reliability of the association measured by relative risks, odds ratios, and hazard ratios we use statistical methods such as p-values and 95% confidence intervals (CIS.)

i. P-values

P-values are a statistical measure that help us understand whether an observed effect is likely to be due to chance or not. When we conduct a study, we want to determine if the results we see are meaningful and not just random fluctuations. Epidemiologic studies are designed to test a null hypothesis. For example, let us posit that we are testing the effects of a new drug in treating a given disease. The null hypothesis may be: the new drug is no more effective at treating the disease than the old drug. When the study is concluded the results tell us that the new drug was twice as effective as the old drug (RR 2.0) at treating the disease and the p-value = .04. The p-value tells us, assuming the null hypothesis and all assumptions in the model are correct, how closely the data fits with the model. The closer to 1 the p-value is, the more closely the data fits the model. In this example the data did not fit the model and therefore, we can be confident that the results were not the result of chance.

The modern approach is not to treat p-values—and in particular, a p-value 0.05—as a touchstone for whether a result is valid. This is consistent with the general approach of interpreting the results of

observational studies in the broader context of biological plausibility, prior knowledge, and other relevant factors. This means that epidemiologists are often less concerned with the precise p-value (which may suggest a yes/no answer that cannot be inferred from a single study) and more interested in understanding whether the results are consistent with what we know about the biology of the disease or exposure being studied, as well as with the findings of other similar observational studies. For example, if multiple studies have consistently found an association between prenatal exposure to a certain chemical and an increased risk of a particular birth defect, even if the p-value is 0.06, epidemiologists may still conclude that there is a true association due to the consistency of the findings and the underlying biological mechanisms.

ii. Confidence Interval

A 95% Confidence Interval (CI) is a range of values calculated to estimate how accurate a result from a study is likely to be. It means that if we repeated the study many times, the true value of what we are trying to measure would fall within this range 95% of the time. For example, let us say a study found that taking a certain medication during pregnancy is associated with a 2-fold increased risk of a child developing a certain condition. The 95% CI would give us a range of values, within which the true increased risk is likely to be. If the 95% CI was 1.5 to 2.5, it would mean that there is a high degree of confidence that the true increased risk is between 1.5 and 2.5 times higher.

The use of 95% CIs is common practice in epidemiology to help interpret study results and assess the level of uncertainty. They provide a range of values that can help researchers and clinicians understand the precision of a study's findings, and how much we can rely on them to make decisions about prevention, diagnosis, and treatment.

i. Sample Size

Sample size in an observational study refers to the number of individuals or units included in the study sample. In observational studies, researchers observe and collect data on individuals or groups of individuals without intervention or manipulation. The sample size is a critical aspect of observational studies as it determines the precision, reliability, and statistical power of the study findings.

A larger sample size generally increases the statistical power of the study and reduces the margin of error, increasing the likelihood of detecting a true association between exposure and outcome. A small

sample size, on the other hand, can result in imprecise estimates, reduce the study's reliability, and increase the likelihood of false-negative or false-positive results.

The appropriate sample size for an observational study depends on several factors, including the research question, the variability of the outcome or exposure, the expected effect size, and the level of statistical significance desired. Researchers often conduct power analyses to estimate the minimum sample size required to detect an effect of a given magnitude with a desired level of statistical power.

j. Exposure-Response

The exposure-response relationship—often called dose response or biological gradient—is a concept used in epidemiology and toxicology to describe the relationship between the amount or level of exposure to an agent and the resulting biological response or outcome. In the context of investigating the association between prenatal acetaminophen use and child NDDs, the concept of exposure-response refers to the relationship between the amount and/or frequency of acetaminophen use during pregnancy and the risk or severity of NDDs in children. If an exposure-response relationship is observed, it means that as the exposure level increases, the risk or severity of the outcome also increases, providing strong evidence that the exposure is a cause of the outcome. As explained in greater detail below, studies investigating the association between prenatal acetaminophen use and child NDDs have found that the risk of developing symptoms of NDDs, including ASD and ADHD, increased with increasing dose and frequency of acetaminophen use during pregnancy. This would demonstrate an exposure-response relationship. This provides strong evidence that prenatal acetaminophen exposure is a cause of NDDs in children.

Exposure-response relationships can be linear or non-linear. Linear exposure-response relationships describe a situation where the relationship between exposure and outcome is proportional and consistent across all levels of exposure. In a linear exposure-response relationship, the outcome changes in a linear or straight-line fashion as the level of exposure increases or decreases. For example, in a study investigating the relationship between the amount of smoking during pregnancy and the risk of low birth weight, a linear exposure-response relationship would be observed if the risk of low birth weight increased proportionally with increasing amounts of smoking.

Non-linear exposure-response relationships occur when the relationship between exposure and outcome is not proportional and may follow a curved pattern. Threshold relationships occur when there

is a certain level of exposure below which there is no effect, but above which there is an increasing effect.

For example, in a study investigating the relationship between alcohol consumption during pregnancy and the risk of fetal alcohol syndrome, a threshold exposure-response relationship would be observed if there is no effect on fetal alcohol syndrome risk at low levels of alcohol consumption but once a certain threshold is reached, the risk increases sharply.

Identifying an exposure-response relationship can also provide important information about the safety of an exposure and can help inform public health recommendations and policies. If an exposure-response relationship is observed, it may indicate that reducing exposure levels or avoiding exposure altogether could lead to a decrease in the risk or severity of the outcome.

k. Bias

Bias in epidemiology refers to a systematic error or deviation from the truth in the results of a study, caused by factors other than chance. Bias can occur in any stage of the research process, from study design to data collection, analysis, and interpretation of results. It is important for epidemiologists to be aware of different types of biases and to take steps to minimize their impact on the results of their studies. I review the most common categories of bias and approaches to minimize them in Section F.3.

l. Effect Modification and Interaction

Effect modification occurs when the relationship between an exposure and an outcome is different for different levels of another variable, known as the effect modifier. This means that the effect of the exposure on the outcome varies depending on the level of the effect modifier.

For example, consider a study examining the association between smoking and lung cancer. The effect of smoking on lung cancer risk may be modified by age, such that the association between smoking and lung cancer is stronger among older individuals than among younger individuals. In this case, age is the effect modifier.

While often conflated with effect modification, interaction refers to a different situation when researchers want to obtain the joint effects of two exposures on a disease or outcome.[154] This concept differs from that of effect modification, which separates exposure effects according to another variable. In other words, when evaluating interactions, epidemiologists estimate the risk associated with each of two variables both individually and in combination. When evaluating effect modification, by contrast,

epidemiologists estimate the risk associated with only one variable and its variation across the strata of a second variable.

Identifying effect modification or interaction is important because it means that the relationship between the exposure and the outcome is not the same for all individuals and may require different strategies for prevention or treatment. Failure to account for effect modification can result in inaccurate estimates of the effect of the exposure on the outcome and can lead to incorrect conclusions.

m. Exposure Assessment

Exposure assessment is a fundamental aspect of epidemiological research that involves measuring or estimating the degree of exposure to a particular factor or agent. Researchers use various methods to assess exposure, such as self-reported use, prescription records, or biomarker analysis of acetaminophen levels in biofluids/materials, such as cord blood and meconium.

It is important to recognize the potential for exposure misclassification. Exposure misclassification can occur in two forms: differential and non-differential. Non-differential misclassification occurs when the misclassification of exposure is similar between cases and controls, leading to biased results toward the null (or a reduction in the observed association between exposure and outcome). In that situation, the study would underestimate the strength of the association, *i.e.*, the association is in truth stronger than that estimated by the study and may exist even if the study returned no statistically significant association. This is more common. Differential misclassification occurs when the misclassification of exposure is different between cases and controls, leading to biased results away from the null (or an increase in the observed association between exposure and outcome.) In that situation, the study would overestimate the strength of the association, *i.e.*, the association is in truth weaker than that estimated by the study. This is less common because most classification issues are not correlated with exposure. In most acetaminophen studies, because information is prospectively obtained, any exposure misclassification would be non-differential and bias the results toward the null, *i.e.*, underestimate the association.

Recall bias is a common type of information bias that leads to differential exposure misclassification in studies relying on self-reported past exposure. Recall bias occurs when participants recall their exposures differently depending on their disease status, leading to biased results. This can be a particular problem if studies investigating the association between an exposure and a disease are based

on self-reported assessment of exposure collected after the diagnosis of the disease. Fortunately, this type of bias is all but absent in this literature, because of the prospective design employed by the studies: the mother's exposure to acetaminophen was measured *before* assessing whether the child developed neurodevelopmental symptoms.

As explained above, in studies such as the ones in this case where exposure information is obtained prospectively, any bias would be toward the null, *i.e.*, underestimating the observed association/risk.

n. Diagnosis and Classification of Disease Outcome

Misclassification of disease outcome refers to errors in the diagnosis or classification of the health condition or disease of interest. Misclassification can occur if the outcome is incorrectly diagnosed, or if different diagnostic criteria are used across study participants. Misclassification can also occur if the outcome is not accurately recorded or if different sources of data are used to define the outcome. Unless there is some reason to think that this misclassification is related to the exposure, misclassification of disease outcome will bias the results toward the null. In the acetaminophen studies, there is no reason to suspect that misclassification would be related to exposure. Therefore, any bias would be expected to be toward the null.

2. Types of Epidemiologic Studies Investigating the Associations of Prenatal Acetaminophen Use on the Developing Brain

Epidemiologists have conducted various types of epidemiologic studies to investigate the association between prenatal acetaminophen exposure and the risk of NDDs in children.

a. Case-Control Studies

Case-control studies are a type of observational study design used to investigate the relationship between an exposure and an outcome, such as the association between prenatal acetaminophen use and child NDDs. In a case-control study, researchers identify two groups of individuals: cases, who have the outcome of interest, and controls, who do not have the outcome. The researchers then gather and compare the exposure history of the cases and controls to determine whether there is an association between the exposure and outcome.

Case-control studies are often used when investigating outcomes that are less prevalent in the background population.

b. Cohort Studies

Cohort studies are a type of observational study that follow a group of individuals over a period of time to determine whether certain exposures are associated with specific outcomes. These studies are often prospective, where individuals are enrolled and followed forward in time.

In the case of investigating the association between prenatal acetaminophen use and the risk of NDDs in children, a cohort study would involve enrolling a group of pregnant women and tracking their acetaminophen use during pregnancy. Then, the children born to these women would be followed over time to determine if they are diagnosed with a NDD or neurodevelopmental symptoms. This group would be compared against a group of pregnant women with the same characteristics but who were not exposed to acetaminophen.

Advantages of cohort studies include:

1. Cohort studies can be used to more precisely assess the temporal relationship between exposure to a risk factor and the development of a disease or health outcome. This is because the exposure is typically measured before the outcome occurs, reducing the potential for recall bias and reverse causality.

2. Cohort studies can provide information on the incidence and natural history of a disease or health outcome over time.

c. Components to both Case-control and Cohort Studies

The accuracy and reliability of these studies is in part dependent on the accurate and complete ascertainment of cases. In case-control studies, the goal is to identify all cases of NDDs within a given population and include as high a percentage of them as possible in the study. Similarly, controls should be free of NDDs and as similar as possible to the cases, except for the exposure under investigation. In cohort studies, it is important to follow all individuals over time to determine how many develop NDDs and to obtain precise exposure information from both cases and non-cases through detailed questionnaires.

The accurate and complete ascertainment of cases. In case-control studies, this means that all cases of NDDs should be identified in a given population and as high a percentage of them should be included in the study as possible. For instance, in a study of diagnosed ADHD cases, ideally all the ADHD cases should be ascertained and accounted for. The controls should be free of an ADHD diagnosis and should

be as similar as possible to the cases except for the exposure under study. In cohort studies, this means that all individuals should be followed over time to determine how many were or were not diagnosed with ADHD. For both types of studies, cases should be confirmed with reasonable certainty.

d. Determination of Exposure

In both case-control and cohort studies, it is important to consider the accuracy of the determination of the exposure. Most studies on the association between prenatal acetaminophen use and NDDs, including ADHD and ASD, relied on maternal self-reporting of prenatal acetaminophen use, and data was collected at various time points, including early pregnancy, middle pregnancy, and after delivery. Prospective data collection strategies reduce the risk of recall bias. Recall bias typically occurs in case-control studies in which exposure to acetaminophen is collected after the mothers have learned about the disease of their children and are likely to recall more accurately or even overreport their use of acetaminophen during pregnancy (see recall bias section above). Conversely, in prospective studies, where the exposure is collected before any diagnosis is made, any information error is expected to be non-differential and bias results towards the null, because the error tends to dilute the differences between mother-child pairs with and without the disease, rather than artificially causing them. As discussed more fully later in this report, several studies used more nuanced operationalizations to assess exposure-responses, cumulative exposures, and plausible critical development periods. Directly measured acetaminophen or metabolite levels were used in some studies reviewed to assess prenatal acetaminophen exposure. These studies provide objective measurement of exposures and have been therefore considered to have higher quality in terms of exposure assessment.

For both case-control and cohort studies, the populations should be well-characterized, so that any potential confounding variables can be accounted for in comparing exposure rates of cases and non-cases.

e. Meta-Analyses.

Meta-analysis is a statistical technique used to combine and analyze results from multiple independent studies on a particular research question. It involves acquiring and combining results from individual studies to estimate a summary effect size, which is a measure of the magnitude and direction of the association between two variables. Meta-analyses are most often conducted by using results published in individual papers from each of the studies of interest and do not require the involvement of the teams that conducted such studies.

Meta-analyses are important because they can provide a more precise estimate of the true effect size of an association, by synthesizing data from multiple studies and reducing random error. This can help to resolve inconsistencies or conflicting findings across individual studies, and to detect small but clinically significant effects that may not be detectable in individual studies due to limited sample size or power, *i.e.*, the ability to identify a statistically significant risk when there is in fact a difference between the two comparison groups.

In the case of investigating the association between prenatal acetaminophen use and neurodevelopmental outcomes, particularly ADHD and ASD, meta-analyses have been used to synthesize and analyze the existing evidence from multiple observational studies. This approach has allowed researchers to examine the overall strength and consistency of the association across different populations, study designs, and methods of exposure and outcome assessment.

f. Systematic Reviews

A systematic review is a method to collect and assess all available empirical evidence that fit within pre-specified criteria to answer a specific research question. Systematic reviews are marked by a detailed and comprehensive search strategy that is set out a priori. This means there must be a pre-defined eligibility criteria for studies that is clearly stated prior to undertaking the literature search. This helps reduce bias by identifying, rating, and synthesizing the relevant science/literature on a topic.

Like meta-analyses, systematic reviews are an important and effective tool to assess an association by synthesizing and grading data from multiple studies. There have been a number of important systematic reviews that assess the association between acetaminophen and neurodevelopmental outcomes, including ADHD and ASD.

g. Umbrella Reviews

Umbrella reviews are a method to collect and assess systematic reviews and meta-analyses that fit within a pre-specified criteria to answer a specific research question. They are an important tool to assess epidemiological associations of exposures. As a general matter, it is only appropriate to conduct an umbrella review when there are multiple systematic reviews and/or meta-analyses on a specific research topic. I note some informative umbrella reviews of the association between acetaminophen and NDDs here.

h. Retrospective and Prospective Study Design

Epidemiological observational studies can use a prospective or retrospective study design to investigate the relationships between exposures and outcomes/diseases. The two types of studies differ in terms of the timing of data collection on the exposures and/or outcomes/disease.

Cohort studies are most often prospective while standard case-control studies are retrospective. Cohort studies may also be retrospective depending on the timing of data collections. Some lesser used variations of the case-control design, *e.g.*, case-control studies nested in a cohort, may use a prospective design.

i. Retrospective and Prospective Design of Cohort Studies

A prospective cohort design is a study in which a group of individuals who are initially free of a disease or health condition are followed over time to observe the occurrence of the disease or condition. The study first identifies a group of individuals (the cohort) with the exposure of interest, such as smoking or a particular occupation, and another group without that same exposure. These individuals are then followed over a period of time, during which data on outcome status (*e.g.*, the appearance of a disease) are collected. The purpose of the study is to determine whether the exposure is associated with an increased or decreased risk of developing the outcome/disease of interest.

In contrast, a retrospective cohort design is a study in which the exposure data (and in some cases the outcome data) are obtained from records or other sources that existed before the study began. In this design, the investigator identifies a group of individuals who have been exposed to a particular factor of interest in the past and then identifies a comparison group of unexposed individuals. The exposure and outcome data are then collected from records or other sources, and the study proceeds as in a prospective cohort design. Retrospective cohort studies are useful when a cohort study is not feasible or when it would be too expensive or time-consuming to follow a cohort prospectively.

In the investigation of the association between prenatal acetaminophen exposure and NDDs, investigators using a prospective cohort design identify a group of pregnant women and follow them and their children over time to observe whether children who were exposed to acetaminophen during pregnancy have a higher risk of NDDs compared to those who were not exposed.

In a retrospective cohort design, the investigator might use medical records or other sources of data to identify a group of pregnant women who were exposed to acetaminophen during pregnancy and then

compare their risk of having children with NDDs to that of a group of unexposed women. The exposure (and in some cases the outcome data as well) would be collected from the medical records or other sources, and the study would proceed as in a prospective cohort design.

Prospective and retrospective cohort studies have different strengths and weaknesses. The major strength of a prospective cohort study is the accuracy of data collection with regard to exposures, confounders, and outcomes/disease. But this strength is realized at the cost of an inevitable loss of efficiency for this design is both expensive and time-consuming due to a usually long follow-up period. By contrast, the retrospective design is a very time-efficient and elegant way of answering new questions with existing data, but one has no choice other than to work with what has been measured in the past, often for another purpose (*e.g.*, patient care). Therefore, the exposure, confounding, and outcome/disease data might be incomplete or inaccurate/imprecise. However, retrospective assessments can in some cases produce better data than prospective assessments. For instance, retrospective assessments of medication use based on prescriptions can be more accurate than prospective self-reports when the medication of interest is only or almost exclusively used when prescribed. In the case of acetaminophen, however, most of its use is from over-the-counter formulations, hence prescription data are bound to be incomplete.

ii. Retrospective and Prospective Design of Case-Control Studies

A case-control study is typically retrospective because it involves identifying individuals who have already developed the outcome of interest (cases) and comparing them to a group of individuals who have not developed the outcome (controls). In other words, the study is designed to look back in time to determine the exposure status of both the cases and controls before the outcome occurred. This is in contrast to a prospective study where individuals are followed over time to determine whether they develop the outcome of interest based on their exposure status at the beginning of the study.

In the investigation of prenatal acetaminophen exposure and child's NDDs, a case-control design can be used when it is not practical to follow a large cohort of pregnant women for many years to determine their acetaminophen exposure and whether their children develop NDDs. For instance, this approach has often been used to investigate the association with ASD, which is a relatively rare disorder and therefore requires very large prospective cohort studies to identify a number of cases large enough to provide sufficient statistical power. Cases (children with ASD) and controls (children without ASD) are identified, and the exposure history of their mothers is determined retrospectively. This is typically

done through interviews (self-reports) or by reviewing medical records to determine whether the mothers took acetaminophen during pregnancy. By comparing the exposure history of the cases and controls, the investigators can determine if there is an association between prenatal acetaminophen exposure and NDDs.

However, there are potential limitations to using a retrospective case-control design in this context. For example, the accuracy of recall by mothers or the completeness of medical records could affect the results. Additionally, there could be other confounding factors that may be misclassified or incorrectly measured if they occurred in the past. Despite these limitations, case-control studies are often used in epidemiological research as they can be a practical and efficient way to investigate potential associations between exposures and outcomes.

However, case-control studies, like cohort studies, can be either retrospective or prospective. In a prospective case-control study, the investigator still analyzes participants based on outcome status (cases vs. control), but the investigator must wait for the cases to occur. One example of a prospective case-control design is the nested case-control design. A nested case-control design is a type of case-control study where cases and controls are identified from within a defined cohort of individuals who are being followed over time. In this design, a group of individuals are identified and then followed for the development of a particular outcome or disease of interest. Within this cohort, some individuals may develop the outcome or disease, and these are the "cases" for the study.

For the nested case-control design, controls are selected from the cohort members who did not develop the outcome or disease during the study follow-up period. The key difference between a traditional case-control study and a nested case-control study is that the nested case-control design selects controls from the same cohort as the cases. This allows for more efficient use of the available data and ensures that the control group is more representative of the source population. In a nested case-control study, data on exposure to risk factors can be collected before the development of the outcome or disease, which allows for a more accurate assessment of exposure status. The data collected on risk factors can be used to compare the exposures of cases and controls.

3. Possible Sources of Bias in Epidemiologic Studies

Bias is an important concern in epidemiological studies, as it can lead to inaccurate estimates of the relationship between an exposure and an outcome. There are many sources that can lead to bias in epidemiological studies.

a. Selection Bias

Selection bias occurs when the study population is not representative of the target population, leading to incorrect conclusions about the relationship between exposure and outcome. Selection bias can occur in many ways, such as volunteer bias (people who volunteer to participate in a study may be different from those who do not), referral bias (patients who are referred to a study may have different characteristics than those who are not), or survival bias (when the study population is selected based on survival status, which can lead to overestimation of the effect of exposure on outcome).

b. Information Bias

Information bias occurs when there are errors or inaccuracies in the measurement or reporting of exposure or outcome, leading to incorrect conclusions about the relationship between exposure and outcome. Information bias can occur in many ways, such as recall bias (when participants may not accurately remember their exposure or outcome), measurement bias (when the tools used to measure exposure or outcome are not accurate or reliable), or observer bias (when the observer's knowledge of the exposure or outcome influences their interpretation of the results).

c. A Special Type of Information Bias—Recall Bias

Recall bias is a specific type of information bias that occurs when participants may not accurately remember their exposure or outcome, leading to an incorrect estimate of the relationship between exposure and outcome.

This can lead to systematic errors in the study findings, as individuals may either over- or under-report their exposure, leading to incorrect estimates of the true association between the exposure and outcome of interest. Recall bias can arise for various reasons, including the time elapsed since the event, the emotional intensity of the event (such as the diagnosis of a disease), or the participant's personal beliefs or attitudes. Understanding the potential impact of recall bias is important when interpreting the results of epidemiological studies.

Although not a factor in most of the studies examined in this case, recall bias may occur in non-prospective studies when participants recall their exposure differently (differential recall bias) depending on their disease status, leading to false associations between the exposure and disease (*i.e.*, bias away from the null, see section below). For example, a parent may be more likely to recall an exposure shortly after a child's diagnosis (*i.e.*, an NDD.) The vast majority of studies related to

acetaminophen use are prospective studies. Recall bias is not an issue when the data is collected prospectively, and therefore is not an issue within those studies.

Prospective studies, where data on exposure and outcome are collected as they occur, are less susceptible to recall bias. Specifically, in prospective studies information about the exposure is collected before the disease develops, and is therefore expected to be non-differential, hence diluting the possible associations between the exposure and the disease rather than overestimating it. Therefore, studies that collected information about exposure prior to the outcome, including the majority of the studies relevant to this case, avoid differential recall bias.

d. Confounding

Confounding is a type of bias in epidemiology that occurs when there is a third variable that is related to both the exposure and the outcome being studied. This third variable, also known as a confounding variable, can distort or obscure the true relationship between the exposure and the outcome, making it difficult to accurately estimate the effect of the exposure on the outcome. Confounding can occur when the study population is not randomly assigned to the exposure of interest, which is common in observational studies. For example, a study that examines the association between smoking and lung cancer may be confounded by age, as older individuals are more likely to smoke and also more likely to develop lung cancer.

To minimize the impact of confounding, epidemiologists often use statistical techniques such as stratification, regression modeling, or matching to control for the confounding variable. Stratification involves analyzing the data separately within each level of the confounding variable. This allows epidemiologists to assess whether the relationship between the exposure and outcome differs across strata of the confounding variable. Regression modeling controls for confounding by including the confounding variable as a covariate in the model. This adjusts for the confounding variable and allows the researcher to estimate the association between the exposure and outcome after accounting for its potential impact. Matching involves pairing cases and controls based on the confounding variable to ensure that the groups are similar with respect to the confounding variable, thus reducing the potential for confounding. Controlling for confounding variables is important in epidemiological studies because it helps to minimize the influence of these variables on the association between exposure and outcome. If a confounding variable is not accounted for, it can lead to a biased estimate of the association between the exposure and outcome. This can happen because the confounding variable is associated

with both the exposure and outcome, and therefore can make it appear as if the exposure is causing the outcome, when in fact it is the confounding variable that is responsible. Appropriate statistical techniques can minimize this problem.

Epidemiology studies may also be subject to residual confounding. Residual confounding is a type of confounding that remains in a study even after the researchers have tried to control for potential confounding variables. This can occur because there may be other unmeasured or unknown factors that are associated with both the exposure and outcome and can influence the relationship between them. In other words, even if researchers have taken into account all known confounding factors, there may still be some confounding that is not accounted for. This can lead to biased estimates of the association between the exposure and outcome.

e. A Special Source of Confounding—Confounding by Indication

A particularly important type of confounding in epidemiology is "confounding by indication," which occurs when the clinical indication for selecting a particular treatment also affects the outcome.[156] This type of confounding arises from the fact that individuals who are prescribed a medication or who take a given medication may be inherently different from those who do not take the drug, because they are taking the drug for a reason. In medical terminology, such individuals have an "indication" for use of the drug. Aschengrau and Seage[157] give the example of studies of the association between antidepressant drug use and infertility. The use of antidepressant medications may appear to be associated with an increased risk of infertility. However, depression itself is a known risk factor for infertility. As a result, there would appear to be an association between antidepressants and infertility. One way of dealing with this is to study the association in subjects who are receiving different treatments for the same underlying disease condition.

This type of confounding is of theoretical concern in the investigation of prenatal acetaminophen and NDDs. For instance, women may take acetaminophen during pregnancy because of fever, which may be a risk factor for NDDs. This raises the question as to whether associations between prenatal acetaminophen and NDDs may be confounded by their indication, rather than being a real association.

Fortunately, just as they have for other types of confounding, epidemiologists have developed a range of approaches to identify and limit confounding by indication. These include stratified analysis, adjustment for indication using statistical techniques, including multivariable regression models or inverse probability weights, and using negative control exposures.

Stratified analysis has been used to evaluate confounding by indication in the association between acetaminophen and NDDs. In this case, stratification by fever can help to identify whether fever or acetaminophen use is the main driver of the observed association. For instance, if the association between acetaminophen use and NDDs disappeared after stratifying the study participants based on whether or not they experienced fever during pregnancy, then fever is likely to be the confounding factor and the association between acetaminophen and the disease is explained by confounding by indication. In this case, the association would be found when all participants are analyzed together, but it would not be found within women who had no fever during pregnancy.

On the other hand, if the association between prenatal acetaminophen and NDDs is found in both strata, then acetaminophen use is independently associated with NDDs. That is, because the association between prenatal acetaminophen and NDDs is seen in both fever and non-fever strata, the association exists independently of fever.

Regression models can also be used to adjust for confounding by indication in the association between acetaminophen use and NDDs. To address confounding by indication, epidemiologists can use regression models that include both the exposure of interest (*e.g.*, acetaminophen use) and the indication variable (*e.g.*, fever) as covariates. The model estimates the effect of acetaminophen use on the outcome of interest, while controlling for the indication variable. This approach helps to isolate the effect of acetaminophen use on the outcome, and identify whether the indication variable (*e.g.*, fever) is truly a confounding variable.

Inverse probability weighting is another statistical technique used to control for confounding variables in observational studies. In the context of confounding by indication, inverse probability weighting can be used to adjust for the probability of receiving a treatment (such as acetaminophen) based on the patient's characteristics or the indication for the treatment. For example, in a study examining the association between prenatal acetaminophen use and NDDs, inverse probability weighting can be used to adjust for the likelihood of taking acetaminophen based on the presence or absence of fever during pregnancy. This approach would involve calculating the probability of taking acetaminophen given the presence or absence of fever, and then using these probabilities to weight the analysis. In addition to fever, inverse probability weighting can be used to adjust for many possible variables affecting indication simultaneously. Inverse probability weighting can be a particularly useful approach when stratification or regression modeling is not feasible due to limited sample size or other constraints.

Finally, negative control exposures can be used in epidemiology to identify or exclude confounding by indication, as well as other types of confounders that might be difficult to identify, including for instance those contributing to residual confounding. The basic idea is to look for a relationship between the exposure and the outcome for an exposure that is not plausibly related to the outcome. For example, in the case of acetaminophen and NDDs, Liew et al. (2019),[12] used in a study of prenatal acetaminophen and ADHD two negative control exposures, *i.e.*, taking acetaminophen four years before or four years after pregnancy.[12] Their assumption was that acetaminophen taken by the mothers four years before the pregnancy was too far away from pregnancy to affect the fetus; and that acetaminophen taken by the mother four years after pregnancy only exposed the mother and not the child – as such either negative control exposures had very little/no biological plausibility as a cause of the child's ADHD-related symptoms.

To use negative control exposures, epidemiologists would compare the results obtained when analyzing the relationship between the exposure (acetaminophen during pregnancy) and the outcome (NDDs) with the results obtained when analyzing the relationship between one (acetaminophen taken by the mother four years before the pregnancy) or the other (acetaminophen taken by the mother four years after the pregnancy) of the two negative control exposures and the outcome (NDDs). If the relationship between acetaminophen use and NDDs is found only with the actual exposure of concern (*i.e.*, acetaminophen taken by the mother during pregnancy) but not with the negative control exposures (*i.e.*, acetaminophen taken by the mother 4 years before or 4 years after the pregnancy), this finding helps exclude confounding by indication, as other potential causes of confounding.

f. Bias Away vs. Toward the Null

Biases away and toward the null can be defined more broadly as follows:

Bias away from the null refers to a statistical phenomenon where an observed effect size or association between two variables appears stronger than it truly is. In technical terms, this bias can occur in statistical hypothesis testing when the null hypothesis (*i.e.*, the hypothesis that there is no difference or association between the variables of interest) is rejected even though there is no true effect present.

Several factors can contribute to bias away from the null, including:

1. Sampling bias: If the sample is not representative of the population, it can lead to overgeneralization of the results and bias away from the null.

2. Measurement error: Inaccurate or imprecise measurement of variables (including recall bias) leading to differential error, as explained above, can exaggerate the observed effect size and lead to bias away from the null.

3. Confounding variables: The presence of confounding variables that are related to the exposure and outcome variables but are not accounted for in the analysis can lead to an overestimation of the effect size.

4. Publication bias: Studies that find a significant effect may be more likely to be published, leading to an overrepresentation of studies with positive findings in the literature.

5. Researcher bias: Researchers may have a vested interest in finding a significant effect, leading to unintentional biases in study design or data analysis.

Epidemiologists typically take rigorous steps to minimize bias away from the null when designing and analyzing studies. These steps may include using representative samples, using accurate and precise measurement tools, using assessment of exposures and other variables that are not influenced by the disease status, controlling for confounding variables, and ensuring transparency and objectivity in study design and analysis.

Bias toward the null refers to a statistical phenomenon where an observed effect size or association between two variables appears weaker than it truly is or non-existent when it truly exists. Again, to put it into technical language, this bias can occur in statistical hypothesis testing when the null hypothesis (*i.e.*, the hypothesis that there is no difference or association between the variables of interest) is accepted even though there is a true effect present.

Several factors can contribute to bias toward the null, including:

a. Sample size: Studies with smaller sample sizes may not have enough statistical power to detect a true effect, leading to a failure to reject the null hypothesis.

b. Measurement error: Inaccurate or imprecise measurement of variables leading to non-differential error (as explained above) can obscure a true effect and lead to bias toward the null.

c. Confounding variables: The presence of confounding variables that are related to both the exposure and outcome variables can weaken, when not accounted for in the statistical analysis, the observed association between the two variables.

d. Study design: The choice of study design may limit the ability to detect a true effect.

Epidemiologists typically use rigorous approaches to minimize bias toward the null when designing and analyzing studies. This may include increasing sample sizes, using more accurate measurement tools, controlling for confounding variables, and considering different study designs.

g. Validity of Questionnaire-based Measures of Neurodevelopment, Attention-Deficit/Hyperactivity Disorder, and Autism Spectrum Disorder

Questionnaires are commonly used in epidemiological studies of neurodevelopmental disorders, including ADHD and ASD, to gather information on symptom severity, associated impairments, and potential risk factors. Studies on the associations between prenatal acetaminophen and ADHD or ASD are often centered on ADHD/ASD diagnosis during childhood. Therefore, questionnaires are often administered to the child's mother, parents, or care providers. There are several challenges associated with using questionnaires in ADHD and ASD research that must be considered:

- Parental bias: The parents completing the questionnaires may have their own beliefs and experiences that could influence their responses. This could lead to bias in the reporting of symptoms or behaviors in their child.
- Overreporting or underreporting: Parents may either overreport or underreport their child's symptoms or behaviors. They may over-report in an attempt to get help for their child or underreport due to stigma or denial.
- Limited information on the child's behavior: Questionnaires completed by parents may not provide sufficient information on the child's behavior in other settings, such as at school or with peers.
- Specificity and sensitivity: Questionnaires may not differentiate between ADHD-related symptoms and those related to other disorders or conditions that share similar symptoms, such as anxiety or depression. Similarly, some symptoms associated with ASD, such as social communication deficits and restricted interests, can also be present in other conditions, such as social anxiety disorder or obsessive-compulsive disorder. This can lead to false positives or false negatives. Also, questionnaires may not be sensitive enough to detect subtle or mild symptoms, which could lead to underestimation of the prevalence of ADHD/ASD-related symptoms.

- Social desirability bias: The parents may respond in ways they perceive as socially desirable, leading to inaccurate information and response bias.
- Language and cultural differences: The questionnaire may not be appropriate for or applicable to parents from different cultural or linguistic backgrounds, leading to errors or biases in the reporting of symptoms or behaviors.

Parent reports of NDDs, however, have been shown to be reliable. For instance, Cree et al. (2032),[158] showed that parent-reported diagnoses of ADHD are reliable over time. Although they noted differences in parent-reported diagnosis against Diagnostic and Statistical Manual (DSM)-based criteria, these differences were deemed to reflect children with milder symptoms or treated ADHD rather than actual discordance. The Centers for Diseases Control also noted that parent reports are a valid method of assessing diagnosed ADHD.[158,159]

Parent-reported data have been used to monitor the number of children who have been diagnosed with ADHD. For example, a study by CDC authors, Visser et al. (2016),[160] compared the estimated percentage of children medically diagnosed with ADHD as reported by parents on a national survey to the percentage from a recent study, Getahun et al. (2013),[161] that used administrative data from medical records of a large health plan in California. When the percentage of children was estimated using samples with similar characteristics, the parent-reported ADHD estimate was similar to the ADHD estimate calculated from health plan medical records. Although Getahun and colleagues asserted that studies relying on parent report of ADHD cases overestimated the true prevalence, this CDC study found evidence of convergent validity that demonstrates the appropriateness of parent report for monitoring state-based and national prevalence of ADHD.

In the context of ASD diagnosis, too, parent reports have been shown to be reliable. For instance, Daniels et al. (2012), verified parent reports of child ASD against a national ASD registry and found that information collected from parents aligned well with that found in the registry.[162] The Daniels Study found: “Growing interest in ASD research requires increasingly large samples to uncover epidemiologic trends; such a large dataset is available in a national, web-based autism registry, the Interactive Autism Network (IAN). The objective of the Daniels study was to analyze how parent reports of professional ASD diagnosis compared to the registry’s database via a medical record review on a sample of IAN Research participants. Sixty-one percent of families agreed to participate, 98% (n = 116) of whom provided documentation verifying a professionally diagnosed ASD. Results of this study suggest that

information collected from parents participating in IAN Research is valid, participants can be authenticated, and that scientists can both confidently use IAN data and reliably recruit participants for autism research."

In addition to using parent-based reports, some ADHD studies have used teacher reports of ADHD-related symptoms. For example, Power et al. (1998),[163] a study evaluating the ability of the ADHD rating scale-IV to differentiate children with ADHD from control and to discriminate children with different ADHD subtypes, the authors compared results from the parent teacher versions of this scale. The Power study found that both parent and teacher ratings were significantly predictive of ADHD diagnostic status, however, teacher ratings better predicted how children with ADHD, Combined Type and ADHD, Inattentive Type, would be differentiated from each other. Similarly, in ASD studies, reports from parties other than parents, such as clinicians and health care providers, may help enhance ASD assessment since teachers, and clinicians may differ in their endorsement of specific types of ASD symptoms, likely based on differing interactional settings.[164]

Errors in reporting symptoms or diagnoses of ADHD or ASD can lead to bias in study results, which can often be toward the null. Specifically, if the diagnosis of ADHD or ASD is underreported or overreported, it can lead to the exclusion of individuals with these conditions from the cases or the inclusion of individuals without these conditions, respectively. This can dilute the effect size of the association being studied, making it more difficult to detect a statistically significant association and potentially leading to bias towards the null. These types of errors are almost always non-differential which bias results toward the null, understating the effects.

h. Identification and Control for Bias in Epidemiology Studies

To ensure accurate and reliable results, epidemiologists employ various strategies to mitigate measurement error in both exposure and outcome assessment.

For instance, exposure measurement is one limitation to consider when reviewing the association between prenatal acetaminophen exposure and NDDs. Acetaminophen is available over-the-counter (OTC) as well as by prescription, making it difficult to capture acetaminophen use accurately in observational studies. Studies relying on maternal self-reporting of OTC use are prone to misclassification, including variation in how mothers group acetaminophen exposure into categories (yes/no, dose, frequency, duration). Mothers may also have poor recall of timing, dose, and frequency of use, and may confuse acetaminophen with other analgesics.

It is worth noting that in the absence of differential recall bias, the sources of exposure misclassification reported above are likely to bias the results toward the null, because they cause some users to be classified as non-users and vice versa. When this happens, it can dilute or weaken the true association between the exposure and outcome and cause the results to appear closer to the null, meaning that a weaker or no association is observed. This is because misclassification tends to make children with and without NDDs appear more similar in their prenatal exposure to acetaminophen than they truly are, making it harder to detect a true difference between them.

Therefore, reducing exposure misclassification is important to detect associations between prenatal acetaminophen use and NDDs. Prospective data collection using structured interviews or questionnaires is a common approach to standardizing exposure measurements. Ideally, information about the exposure should be collected as it occurs, which would minimize misclassification. Additionally, providing a pregnancy calendar before the interview can improve recall accuracy. A method that does not depend on maternal recall is the use of pharmacy databases or medical records to obtain acetaminophen use history; however, one limitation of this approach is that acetaminophen is widely available OTC, and these databases do not capture OTC use. To overcome this limitation, some studies have used biomarkers in cord blood plasma and meconium, which provide objective measures of exposure. [26,165]

Similar to exposure misclassification, outcome misclassification can bias the results. Again, diagnosis of NDD is typically performed by health care providers who are expected to be unaware of whether the mothers used acetaminophen during pregnancy. Therefore, any error in the outcome assessment is expected to be independent of the exposure (*i.e.*, non-differential). In this situation, misclassification of the outcome can dilute or weaken the true association between the exposure and outcome and cause the results to appear closer to the null, meaning that a weaker or no association is observed. This is because misclassification tends to make the exposed and unexposed groups appear more similar in their outcomes than they truly are, making it harder to detect a true difference between them.

When it comes to outcome measurement, previous clinical diagnoses from medical records can be used. Patient registries or pharmaceutical databases can be searched for medications used to treat the problem. To the degree that these are comprehensive, they strengthen the methods. However, partial databases or ones that only selectively include some individuals must be given lesser weight. Psychologists, psychometricians, or trained clinicians can also assess the outcome. Another approach is to use the assessment of two or more sources, such as psychologists, teachers, or parents, to ensure

consistency and reduce the impact of bias from a single rater. Also, some studies have used function brain MRI assessments that objectively identify and measure modifications of brain function. By implementing these strategies, epidemiologists can minimize measurement error and increase the validity of their findings.

Finally, epidemiologists use various methods to mitigate the risk of bias in statistical analyses. One common approach is to adjust for potential confounding and risk factors. Adjusting for these factors can help to isolate the effect of the exposure on the outcome. Epidemiologists may also use statistical methods such as propensity score matching or instrumental variable analysis to address confounding or other sources of bias. Additionally, epidemiologists may perform sensitivity analyses to explore the robustness of their findings to different assumptions and methods. Finally, epidemiologists may use meta-analytic techniques to combine results from multiple studies and to assess the consistency of the findings across studies. The appropriate statistical approach to minimize bias depends on several factors including the study design and the specific research question being investigated. By employing these methods, epidemiologists can help to reduce the risk of bias and improve the validity of their statistical analyses.

G. EPIDEMIOLOGIC EVIDENCE ON THE EFFECTS OF PRENATAL ACETAMINOPHEN ON THE DEVELOPING BRAIN

I provide the below summary of epidemiological evidence regarding prenatal use of acetaminophen and neurodevelopmental disorders, specifically ADHD and ASD, but also refer to my summary Table, Appendix 1. As I discuss in Section C., I considered the below evidence, including any authors' conclusions and noted weaknesses and strengths, when undertaking my Navigation Guide and Bradford Hill assessments.

1. Summary of Evidence Regarding Prenatal Use of Acetaminophen and ADHD

a. Original Papers on the Association Between Prenatal Acetaminophen and ADHD

Streissguth et al. (1987),[166] reported the results of a longitudinal prospective study of 355 women pregnant in 1974–1975 and their children. Women were asked about medication use at the 5th month of pregnancy and acetaminophen had been taken by 41% of women during the first half of pregnancy. Children were tested at 4 years of age using an attention test that had been previously proposed by the lead authors of the paper. Maternal acetaminophen use during the first half of pregnancy did not show a statistically significant association with the attention score; however, the direction of the association

was negative, *i.e.*, children exposed to acetaminophen showed lower attention (beta=-3.25, SE=6.92; p=0.64). The dated nature of this study is a major limitation on its usefulness. Comparing the results of the attention test employed in this study with standardized tests in use today is difficult; however, the direction of the association is consistent with that reported by many studies below. Later studies have been highly critical of Streissguth, noting for example, that the study had "limited diagnostic and assessment methods and small cohort size."[17]

Thompson et al. (2014),[15] found "significantly higher total difficulty scores" in children whose mother used acetaminophen during pregnancy—a result not "associated with any of the other drugs" examined in the study. The authors noted that "[t]hese findings strengthen the contention that acetaminophen exposure in pregnancy increases the risk of ADHD-like behaviours"—and supports the claim that these "findings are specific to acetaminophen." The study analyzed data from the Auckland Birthweight Collaborative Study, a longitudinal study that followed 871 infants of European descent in Auckland, Australia. The use of drugs during pregnancy was analyzed in relation to behavioral difficulties and ADHD symptoms measured by parent reports at age 7 and both parent- and child-reports at 11 years of age. The results showed higher total difficulty scores and increased risk of ADHD symptoms in children at both 7 and 11 years of age (Strengths and Difficulty Questionnaire parent report at age 7 and child report at age 11) if acetaminophen was used during pregnancy, but there were no significant differences associated with any of the other drugs. Children of mothers who used acetaminophen during pregnancy were also at increased risk of ADHD at 7 and 11 years of age (Conners' Parent Rating Scale-Revised) although some of the associations were not statistically significant. The authors described their results as "alarming." Strengths of the study include its prospective, longitudinal design and its ability to control for "a wide range of factors that might influence medication-taking in pregnant mothers (*e.g.*, reported fever, inflammatory problems) and ADHD symptoms in offspring (*e.g.*, birthweight, antenatal smoking and alcohol use)"—controls which, compellingly, "had little effect on the size of the effect." Limitations of the study include a moderate loss of the initial population to follow up, lack of data on the ADHD status of the parents, and a European-only dataset that could potentially limit generalizability to other populations.

Liew et al. (2014),[9] "found that prenatal exposures to acetaminophen may increase the risk in children of receiving a hospital diagnosis of HKD or ADHD medication and of exhibiting ADHD-like behavior." The study also demonstrated a clear dose response, with "higher use frequency increasing risk in an exposure-response manner." The study investigated 64,322 mother-child pairs in Denmark enrolled in

the Danish National Birth Cohort during 1996-2002. Acetaminophen use during pregnancy was assessed prospectively via 3 computer-assisted telephone interviews during pregnancy and 6 months after childbirth. The study ascertained outcome using (1) parental reports of behavioral problems in children 7 years of age using the Strengths and Difficulties Questionnaire; (2) retrieved hyperkinetic disorder diagnoses—which are the diagnoses for ADHD in ICD10 (International Classification of Diseases 10th Revision) coding, a common coding list used to report diagnosis for billing, administrative, and epidemiological purposes – using the Danish National Hospital Registry or the Danish Psychiatric Central Registry prior to 2011; and (3) identified ADHD prescriptions (mainly Ritalin) for children from the Danish Prescription Registry. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of hyperkinetic disorder (HR = 1.37; 95% CI, 1.19-1.59), using ADHD medications (HR = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (RR = 1.13; 95% CI, 1.01-1.27). Stronger associations were observed with use in more than one trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes.[2]

This is a study with a very large sample size and very strong methodology. Other strengths include the availability of multiple end points to assess the ADHD outcome—in particular HKD hospital diagnosis and ADHD medication prescription—and prospective data collection via multiple interviews, allowing the study to capture OTC use more easily. The study was also able to adjust "for several indications that might have triggered maternal acetaminophen use in analyses, and results also did not differ for women who did and did not report infections/ inflammations during pregnancy or when controlling for use of common nonsteroidal anti-inflammatory drugs." Limitations include the theoretical possibility of unmeasured residual confounding, and the use of telephone-based interviews that assessed a list of over 40 medications for their use during pregnancy. Moreover, the Danish National Birth Cohort suffered from substantial loss-to-follow-up (60% remained), introducing the possibility of selection bias. Notably, such bias, because it would have missed women with the highest likelihood of having an affected child and also taking acetaminophen, would have biased results toward the null. This approach might be prone to some non-differential misreporting, which would bias the results toward the null and understate the true risk. The study was also unable to precisely measure dosage because mothers were unable to recall this information accurately. Overall, the results of this study strongly support the

[redacted]

association between prenatal acetaminophen and ADHD. The possibility of errors in reporting the use of acetaminophen might have biased the results toward the null. Hence, this study might even have underestimated the risk of ADHD associated with prenatal acetaminophen use.

Liew et al. (2016),[167] presented “evidence that paracetamol use during pregnancy was moderately associated with subnormal attention and executive function in the offspring at age 5,” adding “to the growing body of evidence in the literature suggesting that paracetamol exposure in utero may alter neurodevelopment in the offspring.” The study examined the impact of maternal use of paracetamol during pregnancy on the attention of children at age 5 years. The study involved 1491 mothers and children enrolled in the Danish National Birth Cohort. First-trimester use of paracetamol was associated with poorer attention scores in childhood, and children prenatally exposed to paracetamol were at a higher risk for subnormal overall attention, selective attention difficulties, and parent-rated subnormal executive function. The risks for subnormal overall attention or executive function were elevated with longer duration of paracetamol use in pregnancy. The odds ratios were OR = 1.5, 95% CI 1.0, 2.5 for subnormal overall attention, OR = 1.5, 95% CI 1.0, 2.4 for selective attention difficulties, and OR = 1.5, 95% CI 0.9, 2.3 for parent-rated subnormal executive function. A subset of mothers reported the trimester in which they used acetaminophen; trimester specific ORs where in overall stronger (up to OR=2.8 for sustained attention and acetaminophen use in the first trimester) than those for ever/never use during pregnancy; it is possible that these stronger associations reflect better recall and lower misclassification of the drug use. Also, the study showed an exposure-response relationship between acetaminophen use and impaired global attention; per each week of use of acetaminophen during pregnancy, the study reported a 6% increased risk in impaired attention (OR=1.06; 1.00, 1.13; p=0.05) and a 7% increased risk (OR=1.07; 95% 1.01, 1.14; p=0.02) for parent-rated subnormal executive function. The study suggests that maternal paracetamol use during pregnancy may be associated with poorer attention and executive function in 5-year-olds. Strengths of the study include its prospective design, attention-function tests administered by trained psychologists blinded to the exposure status, measures of executive function obtained from parents and teachers independently, and the ability to control for a very large number of confounders, including maternal IQ, maternal mental health, parental education and some important indications of acetaminophen use. Limitations include the theoretical possibility of uncontrolled confounding, exposure misclassification—which would likely bias the results toward the null and understate the true risk—and variability in the testing used for the measurement of children’s functioning.

Avella-Garcia et al. (2016),[168] found that "prenatal acetaminophen exposure" "showed adverse effects on attention-related outcomes" in children. The study assessed in a Spanish birth cohort whether prenatal acetaminophen exposure was associated with adverse neurodevelopmental outcomes in children at 5 years of age. 1,382 mother-child pairs were included in the analysis of ADHD symptoms and 40% of the mothers reported using acetaminophen during pregnancy. The actual average age at the time of neuropsychological testing was 4.8 years. The study found that ever-exposed offspring had a non-significant higher risk of ADHD (incidence rate ratio [IRR]=1.25, 95%CI: 0.93–1.69) and a significantly higher risk of presenting hyperactivity/impulsivity symptoms (IRR = 1.41, 95% CI 1.01-1.98). The risk of hyperactivity/impulsivity symptoms increased with frequency of use. The study was well designed, conducted a comprehensive assessment of confounders, including confounding by indication (multiple confounders were both adjusted for in multivariable models and used in separate analysis as stratification variables), and had rich data.

One major limitation is that ADHD symptoms were evaluated when children were 4.8 years in average, when most cases of ADHD might still be hard to diagnose. The timing of the visit might have reduced the number of cases identifiable at the time and caused an intermixing of future cases with controls, resulting in a reduced strength of association in the relative risks reported (*i.e.*, bias toward the null). The authors noted that residual confounding by indication was theoretically possible but noted that "this is unlikely to be a major concern" given that "sensitivity analyses regarding maternal illness and the indication for acetaminophen use hardly changed the results." Another limitation was that the authors were unable to evaluate the effect of dosage "because of mothers' difficulties in recalling the dose taken" and the possibility of non-differential exposure misclassification. A final, and substantial concern is the modest sample size, which would have limited precision and the likelihood of demonstrating statistically significant associations.

Ystrom et al. (2017)[11] found that "long-term maternal use of acetaminophen during pregnancy is associated with ADHD in offspring," even "after adjusting for potential confounders, including parental symptoms of ADHD and indications of acetaminophen use." The Ystrom study examined the relationship between maternal and paternal use of acetaminophen and attention-deficit/hyperactivity disorder (ADHD) in offspring, while accounting for familial risk and reasons for acetaminophen use. Diagnoses from the Norwegian Patient Registry were analyzed for 112,973 offspring, of which 2,246 had ADHD. The analysis revealed that any prenatal maternal use of acetaminophen during pregnancy was associated with a 12% increased risk of ADHD (HR = 1.12, 95% CI: 1.02-1.24). One unique feature of this

study is that it collected detailed information about acetaminophen use, including the total number of days of use. The risk of ADHD increased with the total number of days of acetaminophen use (see table below) providing compelling evidence of dose response. The highest risk of child's ADHD was found in women who reported 29 days or more of use during pregnancy (HR=2.20, 95% CI: 1.50=3.24), indicating a more than doubling of the risk of ADHD.

Number of days of maternal acetaminophen use during pregnancy	HR (95% CI)
No use	1.00 (reference)
1-7 days	0.90 (0.81–1.00)
8-14 days	1.18 (0.98–1.42)
15-21 days	1.35 (1.00–1.81)
22-28 days	1.60 (0.70–3.69)
29 or more days	2.20 (1.50–3.24)

The Ystrom study authors also conducted stratified analysis by indication, including fever and infections or pain. The HRs for the association between acetaminophen use were similar across these two types of indications, as well as among women who did not specify the reason for taking acetaminophen.

Similar to Liew et al. (2019),[12] the Ystrom study also reported the association between maternal acetaminophen use before pregnancy and child ADHD as a negative control exposure to evaluate whether uncontrolled/unmeasured confounding biased the observed results. Acetaminophen taken before pregnancy (precisely, 6 months before pregnancy) was not associated with child's ADHD (HR=0.95, 95% CI 0.85–1.06). The lack of an association between acetaminophen use before pregnancy and child ADHD provides further assurance that uncontrolled time-invariant factors do not explain the association between acetaminophen use during pregnancy and child ADHD in this study. As the Ystrom study authors put it, this result is "consistent with a causal link." The study did find that "acetaminophen use for <8 days is negatively associated with offspring ADHD indicates that the antipyretic effect could be beneficial with regard to fetal development." The study also found a relationship between paternal acetaminophen use and ADHD, which might "question" "the causal role of acetaminophen in the etiology of ADHD," but the authors noted that even this result might be consistent with a causal link, since "it may be due to male germ-line epigenetic effects as described in endocrine disruption effects of acetaminophen on the human testis."

In addition to the negative-control analysis, other strengths of the Ystrom study include that it is not only one of the largest but also one of the best designed studies investigating prenatal acetaminophen and ADHD. The study used several methods to control bias, including examining confounding by indication thanks to the availability of medication data separately for each indication, using pre-pregnancy use as negative control exposure, and controlling for parental ADHD symptoms. However, one potential limitation of this study stems from the low rates of ADHD diagnosis in this population. Only ~2% of children included in the study had an ADHD diagnosis and the authors projected that only 4% of the children would receive an ADHD diagnosis by the time they all reached age 13. This is about 2-3 times lower than the rates commonly observed in North America and most other European countries, hence suggesting that ADHD was underdiagnosed or underreported in this population. It is worth noting that, underdiagnosis/underreporting is likely to be non-differential relative to acetaminophen use during pregnancy and the resulting bias is likely to be toward the null. Therefore, it is likely that the association between ADHD and prenatal acetaminophen use is higher than the estimates provided by this study. In addition, the study was not able to adjust for the severity of each condition indicative of acetaminophen use, the ADHD diagnosis was based on a diagnosis by a specialist in the Norwegian health care system, and the precise population used limits generalizability of the results.

Tovo-Rodrigues at al. (2018),[169] investigated the association between prenatal exposure to acetaminophen and emotional and behavioral problems at ages 6 and 11 in the southern Brazilian city of Pelotas. 27.5% of mothers used acetaminophen during pregnancy. Emotional problems at 6 and 11 years were 13.6% and 19.9%, respectively, and hyperactivity problems were 13.9% and 16.1%, respectively. In boys, intrauterine exposure to acetaminophen increased the odds of hyperactivity/inattention (OR = 1.42; 95% CI: 1.06–1.92) at age 6. At age 11, a small decrease in the effect was observed (OR = 1.25 (95% CI: 0.95–1.65) for hyperactivity/inattention in boys. No association was observed for girls at both ages. However, the quality of this study is questionable based on the low proportion of self-reported acetaminophen use. The authors compared the level in this cohort (27%) to independent data in the region (51%) and concluded that acetaminophen use during pregnancy was underreported. The exposure assessment was based on an open-ended question with no collection of dose, duration, or timing. Misreporting is likely to have diluted the effects, resulting in a weaker association.

Gustavson et al. (2019),[170] "investigated associations between maternal fever and ADHD among offspring." The study used data from the "Norwegian Mother and Child Cohort Study, including more than 114,000 children."[3] The study found that children exposed to maternal fever in the first trimester were at a higher risk of being diagnosed with ADHD—and that repeated exposure to maternal fever further increased the risk. But "[t]here was no association between fever and hyperactivity/impulsivity after adjusting for covariates." The authors also examined whether use of acetaminophen modified that risk but found no evidence that it did: "results were similar whether the mother had taken acetaminophen for their fever or not." Strengths of the study include its large sample size, prospective data collections, and repeated measures of fever during pregnancy. Limitations include a low participation rate and underrepresentation of younger women, smokers, and women with lower education levels. The study also was not designed to assess the link between acetaminophen and ADHD—rather the focus was on examining the link between fever and ADHD. The study also did not provide any data on the effect of acetaminophen on women who take acetaminophen for indications other than fever, *e.g.*, pain relief. This severely limits the application of these findings to this case.

Chen et al. (2019),[171] investigated the association between prenatal exposure to acetaminophen and ADHD risk in the Taiwanese population. The study identified 950 mother-child pairs with ADHD and 3,800 matched control pairs from the Taiwan Longitudinal Health Insurance Database, which offers medical care coverage to all residents of Taiwan. Maternal use of acetaminophen was assessed in the first trimester, second trimester, and third trimester of pregnancy and over the period from 3 months before pregnancy to the date of last menstrual cycle. The study found that exposure to acetaminophen in the second trimester (OR = 1.19; 95% CI, 1.00-1.40), both the first and second trimesters (OR = 1.28; 95% CI, 1.00-1.64), or in any trimester (OR = 1.20; 95% CI, 1.01-1.42) was associated with an increased risk of ADHD in offspring. Sensitivity analysis excluding gestational infections and maternal mental health disorders confirmed this association (OR = 1.33; 95% CI, 1.04-1.69). However, this paper has some limitations, particularly related to lack of clarity about which variables were included as covariates in the logistic regression models. In the study, controls were matched to cases based on mothers' ages, children's sex and ages, mothers' age during pregnancy, income, and urbanization level. However, the list of variables included in the model is described as "demographic data (age, sex, income, level of urbanization), gestational infections, comorbid perinatal conditions and maternal mental health

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disorders." It is not clear whether all the matching variables were included as covariates in the model. If not, the risk estimates might be biased toward the null. In addition, the study noted that prevalence of ADHD might be underestimated in the relevant database, acetaminophen use was likely underestimated due to inability to capture over-the-counter use, and lack of diagnosis for some ADHD cases, all of which would likely bias the association toward the null. Also, the paper did not adjust for conditions that might have brought on the use of acetaminophen, such as fever.

Leppert et al. (2019),[172] was not conducted as a study of the association of prenatal acetaminophen and ADHD. Information about this association was only included as supplemental materials in an appendix separate from the paper. Indeed, the study aimed to investigate whether maternal genetic factors (polygenic risk scores) for NDDs were associated with early-life exposures that have been previously linked to these disorders. The study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK and analyzed 7921 mothers with genotype data. The results showed that maternal risk alleles for ADHD were associated with certain prenatal factors, such as infections, use of acetaminophen during late pregnancy, lower blood levels of mercury, and higher blood levels of cadmium. The appendix included results from a data analysis showing the associations between 30+ risk factors, including prenatal acetaminophen, and ADHD. Prenatal acetaminophen was associated with ADHD risk at age 7 (RR=1.45; 95% CI, 1.18-1.78). However, this analysis, because of the descriptive, supportive role it had in this paper, was only adjusted by child's age at the time of ADHD assessment and sex. This level of adjustment is not adequate to control for potential confounding. Therefore, although it did demonstrate an increased risk of ADHD for women who took acetaminophen while pregnant, in light of its limitations, this study provides limited evidence proving or disproving the association of prenatal acetaminophen with ADHD

Liew et al. (2019),[12] "found an association between maternal use of acetaminophen at the time of pregnancy and risk of ADHD diagnosis in offspring." The study investigated the association between prenatal acetaminophen and ADHD and used an advanced method, negative control exposure (NCE), to evaluate whether uncontrolled/unmeasured confounding biased the results. The study included 8,856 children born to women enrolled in the Nurses' Health Study II cohort in the Boston area. Information on regular maternal acetaminophen use was collected prospectively in biennial questionnaires, and a total of 721 children (8.1%) in the cohort had been diagnosed with ADHD as reported by the mothers. The authors evaluated the associations between maternal acetaminophen use and ADHD during different exposure periods, including periods – such as maternal use of acetaminophen 4 years before

and 4 years after pregnancy – expected to be negative. The NCE analysis suggested that only acetaminophen use at the time of pregnancy was associated with childhood ADHD (odds ratio = 1.34, 95% confidence interval: 1.05, 1.72). The effect estimates for the two NCE periods (*i.e.*, maternal use of acetaminophen about 4 years before and 4 years after the pregnancy) were null. In other words, this study found that acetaminophen use *before* and *after* pregnancy was *not* associated with ADHD, but acetaminophen use *during* pregnancy *was* associated with ADHD. This is powerful evidence against the idea that confounding is to blame for the observed association. The authors' findings indicated that prenatal acetaminophen exposure may influence neurodevelopment. The lack of an association between acetaminophen use in the pre- and post-pregnancy exposure periods and ADHD provides assurance that uncontrolled time-invariant factors do not explain this association, *i.e.*, it suggests that uncontrolled confounding does not explain the observed association. Strengths of this study included its use of an innovative negative control design to attempt to capture unmeasured confounding, its size, its prospective design, and its ability to directly adjust for a wide variety of potential confounders. Limitations of the study include lack of precise information on timing and dosage of acetaminophen use, possible nondifferential exposure misclassification (which would bias the results toward the null and understate the true risk), the theoretical possibility of residual unmeasured confounding, incomplete prescription data, and reliance on self-reports of ADHD diagnoses by the nurse mothers.

Baker et al. (2020),[4] on which I was a co-author, examined the association between prenatal acetaminophen exposure measured in meconium and attention-deficit/hyperactivity disorder (ADHD) in children aged 6 to 7 years. We also performed brain functional magnetic resonance imaging (MRI) to objectively assess the possible effects of prenatal acetaminophen on the child's brain functions. The study included 394 children, of whom 345 had meconium samples collected at delivery and information on ADHD diagnosis and were part of a prospective birth cohort study conducted in Sherbrooke, Québec, Canada. Acetaminophen was detected in 199 meconium samples (57.7%), and ADHD was diagnosed in 33 children (9.6%). Compared to no acetaminophen, detection of acetaminophen in meconium was associated with increased odds of ADHD (OR, 2.43; 95% CI, 1.41-4.21), with an exposure-response association detected. Specifically, each doubling of acetaminophen levels in meconium increased the odds of ADHD by 10% (OR, 1.10; 95% CI, 1.02-1.19). The brain functional-MRI analysis was based on resting-state brain connectivity, assessed when children were aged 9 to 11 years. Children with acetaminophen detected in meconium showed increased negative connectivity between frontoparietal and default mode network nodes to clusters in the sensorimotor cortices, which are alterations often found in children with ADHD. Indeed, statistical mediation analysis showed that these brain MRI

alterations mediated the effect of acetaminophen on increased child hyperactivity. Strengths of this study include a large cohort size; the ability to make a direct, unbiased, biological measure of fetal acetaminophen exposure; and the use of functional MRI technology to directly measure functional brain connectivity. Weaknesses include the theoretical possibility of unmeasured residual confounding, the possibility that meconium levels reflected acetaminophen administered during labor, and the possibility of prior medication use (including acetaminophen use) in the tested children.

The results of this study are particularly important because they overcome some of the weaknesses of previous studies. Acetaminophen exposure assessment was based on objective measurements of the medication in meconium, hence avoiding possible misclassification based on self-reported use. Meconium is a newborn's first feces. It is a sticky, greenish-black substance that is composed of materials ingested during the time the infant spends in the uterus, including intestinal secretions, amniotic fluid, and shed cells. Meconium starts to form early in the second trimester hence potentially reflecting exposure to acetaminophen during the second and third trimester. Meconium is usually passed within the first few days after birth. The lack of misclassification is likely to explain the higher risk estimates produced in this study, thus also suggesting that studies based on self-reports may severely underestimate the risk. This study also used objective brain functional MRI measurements to assess brain function in children. Functional magnetic resonance imaging is a non-invasive neuroimaging technique that uses magnetic fields and radio waves to measure changes in blood flow in the brain that are associated with neural activity. During a functional MRI scan, the patient lies inside a large tube-like machine that uses a powerful magnet to create a strong magnetic field. Radio waves are then directed towards the patient, which cause the protons in the body to move. As they move, the protons emit signals that can be detected by the MRI machine and used to create a detailed image of the brain's structure and function. Functional MRI is used to map the neural activity associated with different cognitive processes, such as perception, attention, memory, and decision-making. It is also used to diagnose and study neurological and psychiatric disorders, including ADHD. Indeed, in this study functional MRIs assessed connectivity in three classical brain networks often implicated in ADHD, *i.e.*, the default mode, salience/cingulo-opercular, and frontoparietal/central executive networks. Because of the strength of both the exposure and outcome assessments in using meconium and MRI, the study methodology is likely the strongest in the literature.

Gustavson et al. (2021)[173] found that "long-term exposure (29 days or more)" to acetaminophen in utero "was associated with a two-fold increase in risk of ADHD diagnosis." The study did not detect an

increased risk of ADHD diagnosis in children "prenatally exposed to acetaminophen for 28 days or less." The study was conducted in the Norwegian Mother, Father, and Child Cohort Study (MoBa), a large population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Strengths of the study include its prospective cohort design and large size. Limitations include reliance on self-reporting of acetaminophen exposure, the possibility of other forms of non-differential misclassification, and the moderate response rate in the MoBa cohort, which likely under-represents young women, smokers, and women with low educational level. The study also employed a sibling control design, whose strengths and limitations are discussed in greater detail below.

Ji et al. (2020),[165] analyzed 996 mother-infant dyads from the *Boston Birth Cohort* to examine the association between cord plasma acetaminophen metabolites and physician-diagnosed ADHD. The study found that cord plasma biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood ADHD. The study also showed a clear dose response. Compared to children in the first tertile of cord acetaminophen burden—*i.e.*, children who experienced the lowest exposure to acetaminophen in utero—the second tertile (OR = 2.26; 95% CI, 1.40-3.69) and third tertile (OR = 2.86; 95% CI, 1.77-4.67) of exposure were associated with higher odds of ADHD diagnosis, suggesting increased risks of nearly 200%. Sensitivity analyses and subgroup analyses found consistent associations between acetaminophen burden and ADHD across strata of potential confounders, including maternal indication, substance use, preterm birth, and child age and sex; in these analyses, the ORs for ADHD diagnosis across strata of potential confounders varied between 2.3 and 3.5—suggesting an increased risk of 130% to 250%. Limitations of this study include the ability to measure acetaminophen levels in the umbilical cord at only one point in time, the inability to capture all biomarkers, 100% detection of acetaminophen in the sample size (which would bias results toward the null since there was no truly unexposed group), the theoretical possibility of residual confounding, and limitations on generalizability given the population studied.

One major strength of this study comes from the measurements of acetaminophen in cord blood, which is blood from fetal circulation. Cord blood measurements are a more accurate means to assess prenatal exposure of the child to acetaminophen compared to information about maternal use of the medication because cord blood provides an objective measure of fetal exposure. Maternal self-report of medication use during pregnancy may be prone to recall bias, underreporting, or overreporting hence potentially causing bias either away or toward the null. Additionally, maternal use of acetaminophen does not directly assess the extent to which the fetus is exposed to the medication. By measuring

acetaminophen and its metabolites in cord plasma, researchers could directly assess the fetal exposure to the medication and obtained a more accurate estimate of the association between prenatal exposure to acetaminophen and child's ADHD. There are limitations to consider when interpreting the results of this study. Firstly, the study only measured cord plasma acetaminophen from cord blood at birth, which may not fully reflect prenatal exposure to acetaminophen and would have biased results toward the null. Since the half-life of acetaminophen in adults is less than three hours, the cord plasma measurement may only reflect maternal use of acetaminophen during the peripartum period. Additionally, the study reported 100% detection of acetaminophen in cord plasma, which contradicts the common knowledge that only about half of pregnant women take acetaminophen, and certainly much less during the peripartum period. This finding may be explained by exposure to acetaminophen through other sources such as drinking water.[174] Alternatively, the author may have used in their analysis values below the detection limit of the assay, although they do not report the actual concentration of acetaminophen measured but only their distribution (see Supplementary materials to the paper). Nonetheless, the authors performed a tertile analysis that grouped the acetaminophen levels into three groups (low, medium, and high), which may have protected against bias caused by the limitations of the assay used, because the analysis did not use the actual values, but grouped the acetaminophen levels false positive findings. Results from this dataset were also reported earlier in a lower tier journal.[175] Based on my assessment and comparison of the two publications, I concluded that the two papers report essentially the same data and results, although they show differences in the data analysis approach and inclusion criteria. In keeping with the approach set forth above, I have focused on the most recent of the two papers in my review. It is again striking that the risks reported in this paper are substantially higher than those reported in papers utilizing less-direct methods of exposure classification (*e.g.*, self-reporting). This suggests that exposure measurements in other papers are biasing the results toward the null—likely substantially—rather than away from it, thereby underestimating the true risk.

Sznajder et al. (2022)[1] "found an association between acetaminophen use [by the mother] and child behavioral problems at the age of 3 years." The study analyzed data from a prospective cohort of 2,423 mother-child pairs in Pennsylvania, USA. Of those, 2400 had data on the child's attention. Mothers were interviewed during the third trimester of pregnancy and 41.7% of them reported acetaminophen use during pregnancy. Children were examined when they were 3 years old. Children exposed to acetaminophen during pregnancy scored significantly higher on three out of seven Child Behavior Checklist (CBCL) syndrome scales, specifically on withdrawn, sleep problems, and attention problems. It

is worth noting that the CBCL attention scale has been shown to be well correlated with ADHD diagnosis in children.[176] After adjusting for prenatal stress and other factors, the prevalence of sleep problems (OR = 1.23, 95% CI = 1.01-1.51) and attention problems (OR = 1.21, 95% CI = 1.01-1.45) remained statistically significantly higher in children exposed to acetaminophen. Specifically, the attention problem analysis was adjusted for infection, trouble sleeping, thyroid conditions, maternal age, insurance coverage, alcohol, anxiety/depression, and stress. Additional potential confounders were evaluated but not adjusted for due to lack of association with the exposure and/or the outcome or because of high collinearity with the exposure (fever). This study suggested that there is a higher risk of attention problems in children exposed to acetaminophen during pregnancy, even after adjusting for prenatal stress and other factors. Strengths of the study include the longitudinal design, large sample size, and assessment of important covariates, such as stress during pregnancy. Limitations of the study include inability to directly measure acetaminophen exposure during pregnancy, no measurement of acetaminophen use during the last weeks of pregnancy, behavioral assessments conducted by the mother and child rather than a physician, the theoretical possibility of unmeasured confounders, and a patient cohort that might not produce generalizable results in light of higher socioeconomic status.

b. Meta-Analyses of Published Studies Regarding the Association Between Prenatal Acetaminophen and ADHD

Masarwa et al. (2018),[24] found that "Acetaminophen use during pregnancy is associated with an increased risk for ADHD, ASD, and hyperactivity symptoms"—a result the authors described as "concerning" and "alarming" when taken in conjunction with results from other studies. In performing the meta-analysis, the authors searched MEDLINE, Embase, and Cochrane databases for relevant studies up to January 2017 and identified six eligible cohorts including a total of 78,133 mother-child pairs, with follow-up periods ranging from 3 to 11 years. The pooled risk ratio for ADHD was 1.34 (95% CI: 1.21, 1.47; I2 = 72%). In meta-regression analysis, the association between exposure and ADHD increased with the child's age upon follow-up (β = 0.03, 95% CI: 0.00, 0.07) and with the mean duration of exposure (β = 0.00, 95% CI: 0.00, 0.01). It is important to note here that this meta-analysis classified all the articles as "retrospective", while my review determined that they were all conducted prospectively (*i.e.*, the outcomes occurred after the enrollment in the cohorts, not vice versa)—perhaps suggesting a semantic difference in terminology. The study authors stated that "[o]ur findings, together with additional recent alarming evidence on the teratogenicity of acetaminophen, warrant further investigation." The authors of Masarwa et al. (2018),[24] updated this meta-analysis in a 2020

publication, Masarwa et al. (2020)[177]; a new meta-analysis that included one more cohort. However, Masarwa et al. (2020) presents conflicting information: The OR for the association between prenatal acetaminophen and ADHD is presented as RR=1.35 (95% Cl 1.25, 1.46) in the abstract and in section 3.6 but as RR 1.31, 95% Cl 1.23, 1.39 in the main figure reporting the results (Figure 1) and in the main results section (section 3.3). Nonetheless, the results of this second meta-analysis, Masarwa et al. (2020), seem to be similar to those of the first Masarwa et al. (2018) meta-analysis, hence confirming those results. Masarwa et al. perform worst-case sensitivity analysis in an attempt to assess theoretical effects from possible unmeasured confounders, selection bias, and exposure misclassification. They acknowledge the E-value they use "is not an observed estimate; rather, it represents a hypothetical effect assessed in a sensitivity analysis." Additionally, the results of their hypothetical sensitivity analysis are that correction for exposure misclassification resulted in an increase in the adjusted RR of about 45%; correction for confounding resulted in a maximum decrease of 19%. In other words, the study underestimated the effect by 45% as a result of bias and overestimated it by 19% as a result of confounding. Thus, the two spurious effects were in opposite directions, with exposure misclassification having the greater impact *i.e.,* even after accounting for both, the result would be a greater bias toward the null. That is, the observed effect was likely an underestimate. Strengths of Masarwa et al. (2020) include a systematic review of the available literature, a random effects method to pool potentially heterogenous studies, a sensitivity analysis, and an investigation into the contribution of relevant covariates via a meta-regression. Limitations include a relatively small number of underlying studies, the small samples sizes, the observational nature of these studies, difficulty in accurately capturing diagnoses for ASD and ADHD, the potential for selection bias in the underlying studies, and the theoretical possibility of some types of unmeasured bias and confounding that suggested caution in making a causal inference.

Gou et al. (2019),[17] concluded that "[t]here is an association between maternal acetaminophen use during pregnancy and the risk of attention deficit/hyperactivity disorder in offspring." Specifically, the study found "that maternal prenatal acetaminophen use is associated with a 25% increased probability of ADHD in offspring in the pooled estimate after adjusting for potential confounding factors." The study searched PubMed, Embase, Web of Science and Cochrane Library and identified eight cohort studies with a total of 244,940 participants. Maternal exposure to acetaminophen during pregnancy increased the risk of ADHD in offspring with a pooled adjusted risk ratio of 1.25 (95% CI = 1.17, 1.34). The p-value for the association between prenatal acetaminophen and ADHD was highly significant ($p<0.00001$). This association was strongest for exposure to acetaminophen in the third trimester of

pregnancy (RR = 1.26; 95% CI = 1.08, 1.47). In addition, a longer duration of maternal acetaminophen use during pregnancy was correlated with a higher risk ratio, demonstrating a clear dose response. Children whose mothers used acetaminophen for 28 or more days during gestation had a higher risk of developing attention deficit/hyperactivity disorder (RR = 1.63; 95% CI = 1.23, 2.16). The authors also created a funnel plot including the studies evaluated and found no evidence of publication bias – hence the studies that were published to date were unlikely to be selectively reported in the literature if they showed an association between prenatal acetaminophen and ADHD.

Strengths of the study include the fact that the papers in the meta-analysis were relatively new and prospective cohort studies, that subgroup analyses could be performed to investigate the contributions of relevant variables, and the ability to categorize duration and timing of acetaminophen exposure by trimester. Limitations include a small number of eligible studies, difference in assessment methods for ADHD, and the theoretical possibility of potentially unidentified or inadequately controlled confounding factors in the included studies that suggest caution "when considering whether this association is causal." Nevertheless, the authors noted that their findings (along with previous ones) "lend weight to the hypothesis that the association is causal" and that "it is overly simplistic and not justifiable to explain away the possibility of causality through confounding factors alone." In other words, the authors doubted whether the repeatedly observed association could be due to confounding alone (rather than causation).

Kim et al. (2020),[178] "aimed to systematically appraise the published evidence of association between potential risk factors"—including prenatal acetaminophen use—"and ADHD." The study performed "an umbrella review of meta-analyses," performing "state-of-the-art methods of umbrella reviews," in which the authors "classified the eligible meta-analyses according to the strength of the evidence." The study ultimately found that the "evidence of association was convincing (class I)" for "maternal acetaminophen exposure during pregnancy (RR 1.25, CI 1.17-1.34)" and concluded that maternal acetaminophen exposure was "strongly associated with ADHD in offspring." In all three subset analyses performed, "there was convincing evidence that maternal acetaminophen exposure during pregnancy was associated with a higher risk of ADHD in offspring." The authors noted that "various potential mechanisms" have been suggested to explain the association—and that these mechanisms are "consistent" with evidence known about acetaminophen's pharmacology. Strengths of the study include its extremely large scale, examination of data from numerous studies, its use of an innovative umbrella-analysis study design, and the "robust associations consistently found across the multiple

studies." Limitations include the observational nature of the constituent studies, which the authors noted do not necessarily imply causality, lack of specificity on certain ADHD symptoms, and the theoretical possibility of some residual confounding. The authors asked for further high-quality primary studies to confirm the findings.

Alemany et al. (2021),[18] found that "children prenatally exposed to acetaminophen were 19% and 21% more likely to subsequently have borderline or clinical ASC (OR = 1.19, 95% CI 1.07–1.33) and ADHD symptoms (OR= 1.21, 95% CI 1.07–1.36) compared to non-exposed children." The study conducted a combined analysis of six European population-based birth/child cohorts, *i.e.*, the Avon Longitudinal Study of Parents and Children (ALSPAC), Danish National Birth Cohort (DNBC), Gene and Environment: Prospective Study on Infancy in Italy (GASPII), the Generation R Study, INMA (including four sub-cohorts), and the Mother–Child Cohort in Crete (RHEA). The six cohorts were in different European countries, including the United Kingdom, the Netherlands, Denmark, Italy, Spain, and Greece. A total of 73,881 mother-child pairs were included in the study. Prenatal and postnatal (up to 18 months) acetaminophen exposure was assessed through maternal questionnaires or interviews. ADHD symptoms were assessed at 4–12 years of age using validated instruments. Children were classified as having borderline/clinical symptoms using recommended cutoffs for each instrument. Analyses were adjusted for child and maternal characteristics along with indications for acetaminophen use. The confounders adjusted for included maternal characteristics, *i.e.*, age at delivery (years), education (low, medium, high), race, pre-pregnancy body-mass index (BMI), alcohol (yes/no), smoking (yes/no) and mental health problems (yes/no) during pregnancy, age at birth (years) and parity (nulliparous, > 1 and > 2), maternal fever (yes/no) and infections (yes/no) during pregnancy, and child characteristics, *i.e.*, sex, age at behavioral assessment (years), cold (yes/no) and respiratory infections (yes/no) in the first 2 years of life. Children prenatally exposed to acetaminophen were 21% more likely to subsequently have ADHD symptoms (OR = 1.21, 95% CI 1.07–1.36) compared to non-exposed children. Boys and girls showed higher odds for ASD and ADHD symptoms after prenatal exposure, though these associations were slightly stronger among boys. Postnatal exposure to acetaminophen was not associated with ADHD symptoms. This is a well conducted meta-analysis with high statistical power, robust methods, and critical precautions to address confounding, including confounding by indication. It is worth noting that although cohorts were based across six different countries with different national languages and cultures and also differed in the prevalence of ADHD symptoms, associations between prenatal acetaminophen and ADHD were largely consistent across cohorts. Limitations of the study include the fact that ASD and ADHD symptoms were assessed by different instruments in the cohorts (although the

authors took care to harmonize instruments), the theoretical possibility of some residual confounding by indication (even though “potential indications for acetaminophen use were included as covariates”), exposure misclassification, the small possibility of some selection bias given loss to follow up in some cohorts, and the theoretical possibility of other residual confounding, even though “results were adjusted by several lifestyles and health factors,” reducing the likelihood of that possibility. Overall, this is a particularly strong study.

The study authors noted that “the consistent associations found across different sensitivity analysis including examining ASC and ADHD diagnosis in the largest cohort makes unlikely that the observed relationship between prenatal acetaminophen and ASC and ADHD symptoms is entirely explained by unmeasured confounding.” The study authors also reviewed some of the well-established Bradford Hill elements—including “coherence,” “biological plausibility,” “consistency,” and “dose-response relationship.” Specifically citing the original Bradford Hill address, the authors noted that these “causal criteria [elements]” were satisfied. The study concludes as follows: “Considering all evidence on acetaminophen use and neurodevelopment, we agree with previous recommendations indicating that while acetaminophen should not be suppressed in pregnant women or children, it should be used only when necessary.”

Ricci et al. (2023),[21] found that “[i]n utero acetaminophen exposure was associated with an elevated risk of ADHD (unadjusted pooled RR 1.32, 95% confidence interval [CI] 1.20, 1.44; I2 = 47%, n = 7 studies), with little difference after adjusting for confounders, including indications for acetaminophen use.” “[T]he strength of the association between in utero acetaminophen exposure and child ADHD was strongest in individuals with the highest duration of exposure, suggesting a dose-response effect.” The study conducted a meta-analysis on prenatal acetaminophen use and ADHD. The authors searched multiple data sources, including OVID for Medline, Embase, and PsycINFO, and EBSCO for CINAHL, from inception to August 18, 2022. Data were extracted using a standardized form created a priori, and quality was assessed using the Systematic Assessment of Quality in Observational Research. Pooled RRs were generated using random-effects models. The meta-analysis included 7 studies for a total of 195,957 mother-child pairs. In utero acetaminophen exposure was associated with an elevated risk of ADHD (unadjusted pooled RR 1.32, 95% CI 1.20, 1.44), with little difference after adjusting for confounders. The adjusted pooled RR was increased after minimal adjustment for maternal and infant characteristics (adjusted pooled RR 1.47, 95% CI 1.12, 1.92; I2 = 80%, 4 studies, n = 122,294), with slight attenuation after further adjusting for confounding by indication (adjusted pooled RR 1.34, 95% CI 1.15,

1.55, I2 = 50%, 4 studies, n = 74,659). The fully adjusted pooled RR was similar in children of 6 years of age and older as in the main analysis that included all children regardless of age. Meta-analysis of studies excluding women with reports of fever also yielded an elevated pooled RR (pooled RR 1.61, 95% CI 1.21, 2.13). This recent meta-analysis supports an association between prenatal acetaminophen and ADHD and shows no evidence of confounding by indication. Strengths of the study include a quality-assessment tool to assess measurement and adjust for confounding by indication, substantial data on medication use, and a specific analysis of the potential for confounding by indication. Limitations include heterogeneity of the quality of studies used in the meta-analysis, restriction to studies written in English, and inability to examine acetaminophen exposure by trimester. The authors noted that their findings were "aligned with prior systematic reviews and meta-analyses, which have suggested an association between in utero acetaminophen exposure and adverse child neurodevelopmental outcomes, with most focusing on ADHD." Given that the strengths were many and the limitations few, this is a particularly strong addition to the literature.

2. Summary of Evidence Regarding Prenatal Use of Acetaminophen and ASD

a. Original Papers on the Association between Prenatal Use of Acetaminophen and ASD

Zerbo et. al. (2013)[179] was a small case control study designed to "assess associations with maternal influenza or fever during pregnancy," in particular ASD and developmental delays. The study found that ASD and developmental delays were not statistically significantly associated with influenza (though the odds ratios were elevated) but were associated with maternal fever during pregnancy, though that risk was attenuated among mothers who reported taking antipyretic medications. Specifically, the study found that "children whose mothers reported fever but took anti-fever medications had comparable odds for ASD as those whose mothers did not have fever during pregnancy." The authors interpreted this study to suggest that use of antipyretic medications during pregnancy may be beneficial to the developing fetus with regard to autism spectrum disorders. This study had serious limitations. This study was not designed to look for a link between acetaminophen and ASD specifically. Instead, its primary purpose was to "investigate the association between maternal influenza infection or fever during pregnancy and risk for autism and developmental delays." The study utilized a case control design—generally considered inferior to the large cohort studies discussed here. The authors noted that the "results [could] potentially be affected by recall bias," and the study was relatively small. The study did not examine the effect of acetaminophen specifically, instead grouping acetaminophen together with a number of other antipyretic medications—including ibuprofen, Excedrin, and many others—

severely limiting the ability of this study to provide reliable evidence on the association between acetaminophen and ASD. Finally, the study focused only on women who had fever and influenza in pregnancy, and not on women who took antipyretic medications for indications other than fever, *e.g.*, minor pain relief.

Avella-Garcia et al. (2016),[168] found that male children "persistently exposed" to acetaminophen in utero "presented [with] more autism symptoms" than unexposed male children—an association that showed a statistically significant trend "by increasing frequency of exposure, suggesting a dose response. The study assessed in a Spanish birth cohort whether prenatal acetaminophen exposure was associated with adverse neurodevelopmental outcomes in children at approximately 5 years of age (mean age of 4.8 years) using the Childhood Autism Spectrum Test (CAST) which quantifies autism spectrum symptoms in children (each point represents one symptom of ASC with a cut-off of 15 or more points, having a 100% sensitivity and 97% specificity for ASD). 1,467 mother-child pairs were included in the analysis of the CAST data and 40% of the mothers reported using acetaminophen during pregnancy. Overall, children who were ever-exposed to acetaminophen during pregnancy did not show any significant difference in CAST scores compared to children who did not (β = 0.08; 95% CI -0.28, 0.44). However, boys ever-exposed to acetaminophen during pregnancy showed an increase in CAST symptom scores (β = 0.63, 95% CI 0.09, 1.18) that differed significantly from the result found in girls, who showed a decrease (β = -0.51, 95% CI -0.98, -0.05) in CAST scores (P interaction = 0.01). The study also found a non-significant increase in CAST for children who had been exposed to acetaminophen at all three trimesters of pregnancy (β = 0.81, 95% CI -0.13, 1.73). This association was statistically significant among boys (β = 1.91, 0.44, 3.38), and this association showed a P for trend = 0.006 by increasing frequency of the exposure across trimesters. In females there was no clear trend by frequency of exposure. I provide additional details on the strengths and limitations of this study above in my discussion of the ADHD-specific literature.

Liew et al. (2016),[180] found that "prenatal use of acetaminophen was associated with an increased risk for ASD in the offspring among those also diagnosed with a hyperkinetic disorder." The study investigated the use of acetaminophen during pregnancy on 64,322 children and their mothers enrolled in the Danish National Birth Cohort (DNBC) between 1996 and 2002. The study participants were followed prospectively for an average of 12.7 years. Information on acetaminophen use during pregnancy was collected through three computer-assisted telephone interviews, and the children were monitored for diagnoses of ASD using records from Danish hospital and psychiatric registries. At the end

of follow-up, 1,027 (1.6%) children were diagnosed with ASD, including 345 (0.5%) with infantile autism. More than half of the women reported using acetaminophen during pregnancy. The study found that prenatal use of acetaminophen was associated with an increased risk of ASD (1.19 (HR=1.19, 95% CI 1.04–1.35). Prenatal acetaminophen was more strongly associated with ASD accompanied by hyperkinetic symptoms (HR=1.51, 95% CI 1.19–1.92), but not with other ASD (HR=1.06, 95% CI 0.92–1.24). Furthermore, longer duration of use, defined as use for more than 20 weeks in gestation, increased the risk of ASD or infantile autism (HR= 1.54, 95% CI 1.18–2.02) and that of ASD with hyperkinetic symptoms almost twofold (HR=1.92, 95% CI 1.20-3.06). Strengths of this study include its use of a prospective design with exposure data collected "through multiple interviews long before ASD diagnosis." The study was also able to conduct a dose-response analysis, albeit one based on total weeks of exposure since the interviewed women were unable to recall the precise dosages taken. The study also had a long follow up period (average of 12.7 years) and was able to control for a large number of potential confounders, but the "results did not change" after adjustment, suggesting that confounding plays a minimal role in the association observed. Limitations include the lack of direct measure of exposure, the lack of precise measurement of acetaminophen dose, and the theoretical possibility of residual confounding, though the control for confounders limits this possibility. As the authors note, if such a theoretical confounder exists, it would "also need to have a *strong* effect only on the hyperkinetic subtype of ASD."

Hornig et al. (2018),[181] was a prospective study performed in a Norwegian cohort designed "to examine whether we could find evidence to support an association of the prenatal occurrence of fever, a common manifestation of infection, with ASD risk." The study found that "[p]renatal fever was associated with increased ASD risk among offspring" with the strongest effects in the second trimester and more muted effects in the first trimester. "Risks were minimally mitigated in women taking acetaminophen for fever in the second trimester." The authors emphasized that they found "only small risk reduction with use of acetaminophen for fever." "None of the women with offspring later diagnosed with ASD used ibuprofen for fever in pregnancy." Strengths of the study include its use of a large, prospective cohort and its use of a data set linked to a patient registry. But the study has significant limitations with respect to the question being examined here. The study was not designed to assess the link between acetaminophen and ASD, but rather to assess the link between fever and ASD. And the study did not provide any data on the link between acetaminophen and ASD in women who took acetaminophen for indications other than fever, *e.g.*, minor pain relief.

Leppert et al. (2019),[172] was not conducted as a study of the association of prenatal acetaminophen and ASD. Information about this association was only included as supplemental materials in an appendix separate from the paper. Indeed, the study aimed to investigate whether maternal genetic factors (polygenic risk scores) for NDDs were associated with early-life exposures that have been previously linked to these disorders. The study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK and analyzed 7786 mothers with genotype data. The results showed little evidence of associations of maternal risk alleles for ASD with early life exposures. The appendix included results from a data analysis showing the associations between 32 risk factors, including prenatal acetaminophen, and ASD. Prenatal acetaminophen was not associated with ASD risk at age 7 (RR=0.76; 95% CI, 0.51-1.13). However, this analysis, because of the descriptive, supportive role it had in this paper, was only adjusted by child's age at the time of ASD assessment and sex. This level of adjustment is not adequate to control confounding. Therefore, this study provides very limited evidence proving or disproving the association of prenatal acetaminophen with ASD.

Saunders et al. (2019),[155] conducted a case-control study on the association of a range of risk factors during pregnancy and autism spectrum disorder (ASD) in children. Among the exposures investigated was acetaminophen/paracetamol use. The study included 215 mothers of children aged 0-10 years, with 107 children diagnosed with ASD and 108 without ASD. ASD diagnoses were reported by the mothers, were made before age 6 years, and also before the study. ASD cases were identified through a variety of means, including on clinical charts at the local hospital in St. John, Canada, four local pediatricians, or because mothers contacted the research team after learning of the study through recruitment posters. The comparison group ('non-ASD') was a random sample of children from the same region of the city and within the same age range as the ASD group selected after they contacted the research team after seeing study recruitment posters. Although the methods are not thoroughly described, the researchers appear to have matched controls to cases by sex and age.

The study purported to find no significant difference between the ASD and non-ASD groups in terms of maternal acetaminophen/paracetamol use during pregnancy. But the paper reports no estimates of the relative risk associated with acetaminophen use, nor the frequency of reported use, but only a non-significant p-value (p=0.657) along with a Pearson Chi-Square estimate. The study has other major flaws that severely affect its quality and validity, including retrospective case-control design with minimal consideration of epidemiological methods, including no consideration of any confounders, retrospective design, selection of controls through means different from those of the cases, and lack of adjustment for

matching variables. Thus, the study quality is extremely low and the results should be weighed accordingly.

Ji et al. (2020),[165] found that umbilical "cord biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood . . . ASD in a dose-response fashion." The study analyzed 996 mother-infant dyads from the *Boston Birth Cohort* to investigate the association between acetaminophen metabolites measured from plasma drawn from the umbilical cord at delivery and physician-diagnosed ASD. The study found that cord plasma biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood ASD in an exposure-response fashion. Compared to children in the first tertile of cord acetaminophen burden, children in the second (OR = 2.14; 95% CI, 0.93-5.13) and third (OR = 3.62; 95% CI, 1.62-8.60) tertiles were associated with higher odds of ASD diagnosis, suggesting increased risks of more than 100% and 200%, respectively. Sensitivity analyses and subgroup analyses found consistent associations between acetaminophen burden and ASD across strata of potential confounders, including maternal indication, substance use, preterm birth, and child age and sex; in these analyses, the ORs for ASD diagnosis across strata of potential confounders varied between 1.6 and 4.1.

One major strength of this study is its use of measurements of acetaminophen in cord plasma, which is plasma from fetal circulation. Cord plasma measurements are a more accurate means to assess exposure of the fetus to acetaminophen compared to information about maternal use of the medication because they provide an objective measure of fetal exposure. Maternal self-report of medication use during pregnancy may be prone to recall bias, underreporting, or overreporting hence potentially causing bias either away or toward the null. Additionally, maternal use of acetaminophen does not directly assess the extent to which the fetus is exposed to the medication. By measuring acetaminophen and its metabolites in cord blood, researchers could directly assess the fetal exposure to the medication and obtained a more accurate estimate of the association between prenatal exposure to acetaminophen and child's ASD. The fact that the risks observed in this and other studies that measured acetaminophen levels directly suggests that studies based on self-reporting are biased toward the null—and that the true risk is higher than reported in those studies. In addition, the link between prenatal acetaminophen exposure and ASD persisted even after adjusting for "maternal fever during pregnancy, which is an indicator for acetaminophen use," and even "after a series of further adjustment of potential confounders and differential inclusions." These results provide further assurance that the association is not the result of confounding. The study also identified "dose-response patterns for cord uncharged

acetaminophen and cord acetaminophen burden with the risk of . . . ASD," indicating that as the amount of acetaminophen in the cord blood increased, so did the risk of ASD for the child.

There are limitations to consider when interpreting the results of this study. Firstly, the study only measured cord plasma acetaminophen from cord blood at birth, which may not fully reflect prenatal exposure to acetaminophen. Since the half-life of acetaminophen in adults is less than three hours, the cord plasma measurement may only reflect maternal use of acetaminophen during the peripartum period. Additionally, the study reported 100% detection of acetaminophen in cord plasma, which contradicts the common knowledge that only about half of pregnant women take acetaminophen, and certainly much less during the peripartum period. This finding may be explained by exposure to acetaminophen through other sources such as drinking water.[174] Alternatively, the authors may have used in their analysis values below the detection limit of the assay, although they do not report the actual concentration of acetaminophen measured but only their distribution (see Supplementary materials to the paper). Nonetheless, the authors performed a tertile analysis that grouped the acetaminophen levels into three groups (low, medium, and high), which may have protected against bias caused by the limitations of the assay used, because the analysis did not use the actual values, but grouped the acetaminophen levels false positive findings. Results from this dataset were also reported earlier in a lower tier journal.[175] Based on my assessment and comparison of the two publications, I concluded that the two papers report essentially the same data and results although they differ in the data analysis approach and inclusion criteria. In keeping with the approach set forth above, I have utilized the most recent of the two papers in my review. Additional discussion of Ji 2020 appears in my above analysis of the ADHD-specific literature.

b. Meta-Analyses of Published Papers Regarding the Association Between Prenatal Acetaminophen and ASD

Masarwa et al. (2018),[24] found that "acetaminophen use during pregnancy is associated with an increased risk for. . . ASD," a result they described as "concerning." The study searched MEDLINE, Embase, and Cochrane databases for relevant studies up to January 2017 and identified five eligible cohorts. However, the authors did not seem to report the total number of mother-child pairs included in the analysis of ASD. The entire paper, which also included meta-analysis of ADHD and emotional problems included 7 cohorts for a total of 132,738 mother-child pairs, but it is not clear how many pairs were included in the ASD meta-analysis. The pooled risk ratio for ASD was 1.19 (95% CI: 1.14, 1.25; I2 = 14%). It is important to note here that this meta-analysis classified all the articles as "retrospective",

while my review determined that they were all conducted prospectively (*i.e.*, the outcomes occurred after the enrollment in the cohorts, not vice versa), perhaps suggesting a difference in nomenclature usage. The strengths and limitations of this study are discussed in greater detail above in my discussion of the ADHD-specific literature.

Alemany et al. (2021),[18] found that "children prenatally exposed to acetaminophen use were 19% more likely to subsequently have borderline or clinical [autism spectrum condition]." "Overall," the authors noted, "our findings provide support for the association between prenatal acetaminophen and ASC symptoms in line with a previous meta-analysis."[177] The authors noted that "[t]hese results replicate previous work and support providing clear information to pregnant women and their partners about potential long-term risks of acetaminophen use."

The study conducted a meta-analysis of six European population-based birth/child cohorts, *i.e.*, the Avon Longitudinal Study of Parents and Children (ALSPAC) Danish National Birth Cohort (DNBC), Gene and Environment: Prospective Study on Infancy in Italy (GASPII), the Generation R Study, INMA (including four sub cohorts), and the Mother–Child Cohort in Crete (RHEA). The six cohorts were in different European countries, including the United Kingdom, the Netherlands, Denmark, Italy, Spain, and Greece. A total of 73,881 mother–child pairs were included in the study. Prenatal and postnatal (up to 18 months) acetaminophen exposure was assessed through maternal questionnaires or interviews. ASD symptoms were assessed at 4–12 years of age using validated instruments. Children were classified as having borderline/clinical symptoms using recommended cutoffs for each instrument. Analyses were adjusted for child and maternal characteristics along with indications for acetaminophen use. The confounders adjusted for included maternal characteristics, *e.g.*, age at delivery (years), education (low, medium, high), race, pre-pregnancy body-mass index (BMI), alcohol (yes/no), smoking (yes/no) and mental health problems (yes/no) during pregnancy, age at birth (years) and parity (nulliparous, > 1 and > 2), maternal fever (yes/no) and infections (yes/no) during pregnancy, and child characteristics, *i.e.*, sex, age at behavioral assessment (years), cold (yes/no) and respiratory infections (yes/no) in the first 2 years of life. Children prenatally exposed to acetaminophen were 19% more likely to subsequently have ASD symptoms (1.19, 95% CI 1.07–1.33) compared to non-exposed children. Boys and girls showed higher odds for Autism Spectrum Condition after prenatal exposure, though these associations were slightly stronger among boys. Postnatal exposure to acetaminophen was not associated with ASD symptoms. This is a well conducted meta-analysis with high statistical power, robust methods, and critical precautions to address confounding, including confounding by indication. It is worth noting that

although cohorts were based across six different countries with different national languages and cultures and also differed in the prevalence of ASD symptoms, associations between prenatal acetaminophen and ASD were largely consistent across cohorts. The strengths and limitations of this study are discussed in greater detail above.

The study authors noted that "the consistent associations found across different sensitivity analysis including examining ASC and ADHD diagnosis in the largest cohort makes unlikely that the observed relationship between prenatal acetaminophen and ASC and ADHD symptoms is entirely explained by unmeasured confounding." The study authors also reviewed some of the well-established Bradford Hill factors—including "coherence," "biological plausibility," "consistency," and "dose-response relationship." Specifically citing the original Bradford Hill address, the authors noted that these "causal criteria [elements]" were satisfied. The study concludes as follows: "Considering all evidence on acetaminophen use and neurodevelopment, we agree with previous recommendations indicating that while acetaminophen should not be suppressed in pregnant women or children, it should be used only when necessary."

Kim et al. (2019),[182] conducted an umbrella review to "study the strength and validity of the suggested environmental risk factors or biomarkers of ASD." The review found an "association of ASD" with (among other things) "acetaminophen exposure during pregnancy." The authors classified the association as "highly suggestive evidence." Strengths include the innovative umbrella-review methodology and the use of strict and objective criteria for assessing the associations demonstrated in the reviewed studies. Limitations include the possibility of bias in the individual studies reviewed, inability to assess the quality of the constituent meta-analyses, inability to adjust for certain environmental risk factors, the theoretical possibility of residual confounding, and a relatively early date (2019) that precedes some of the more well-designed studies on the topic of prenatal acetaminophen use and ASD. Additional details on this study are reported above in my discussion of the ADHD-specific literature.

3. Summary of Evidence Regarding Prenatal Use of Acetaminophen and Neurodevelopment Disorders

The previous sections described the evidence regarding the association of prenatal acetaminophen use with ADHD and ASD. Indeed, most of the studies conducted to date focused either on ADHD or ASD. Because ADHD and ASD are part of a larger group of NDDs, I review here additional data that evaluated the association of prenatal acetaminophen use with other NDDs.

a. Original Papers on the Association Between Prenatal Acetaminophen and Other Neuropsychological and Developmental Disorders.

Streissguth et al. (1987),[166] conducted a prospective study of 1,529 women pregnant in 1974-1975. Forty-one percent of women reported using acetaminophen during pregnancy. Women were asked about medication use at the 5th month of pregnancy and acetaminophen had been taken by 41% of women during the first half of pregnancy. In a selected cohort of 421 offspring examined at 4 years of age, maternal acetaminophen use during the first half of pregnancy was not significantly associated with IQ. Above, in my discussion of the ADHD-specific literature, I discuss the strengths and limitations of this study.

Brandlistuen et al. (2013),[14] found that "paracetamol use during pregnancy was associated with adverse neurodevelopmental outcomes at 3 years of age." The study investigated the potential neurodevelopmental effects of prenatal paracetamol exposure on children at 3 years of age using the Norwegian Mother and Child Cohort Study. The sample included 48,631 children and 2,919 same-sex sibling pairs were used for adjustment of familial and genetic factors. Mothers reported on their use of paracetamol at gestational weeks 17 and 30 and at 6 months postpartum. The analysis showed that children exposed to prenatal paracetamol for more than 28 days had poorer gross motor development (β 0.24, 95% confidence interval (CI) 0.12–0.51), communication (β 0.20, 95% CI 0.01–0.39), externalizing behaviour (β 0.28, 95% CI 0.15–0.42), internalizing behaviour (β 0.14, 95% CI 0.01–0.28), and higher activity levels (β 0.24, 95% CI 0.11–0.38). Children exposed prenatally to short-term use of paracetamol (1–27 days) also had poorer gross motor outcomes (β 0.10, 95% CI 0.02–0.19), but the effects were smaller than with long-term use. The conclusion was that children exposed to long-term use of paracetamol during pregnancy had substantially adverse developmental outcomes at 3 years of age. Strengths of this study include its use of a sibling-controlled design (discussed below), large sample size, and ability to control for systematic measurement errors related to the mother. Limitations of the study include a relatively low participation rate, inability to directly measure dose, the theoretical possibility of residual confounding, though that possibility is substantially less likely given the sibling-control design of this study, and limitations in the data caused by reliance on self-reporting.

Vlenterie et al. (2016),[183] found that "[l]ong-term exposure to paracetamol in utero was associated with modestly increased risks of motor milestone delay and impaired communication skills among children at 18 months." The study investigated the association between prenatal paracetamol exposure and neurodevelopmental problems among children at 18 months of age. Of the 51,200 pregnancies

included in the study, 20,749 mothers (40.5%) used paracetamol at least once during pregnancy. Long-term exposure (≥ 28 days) to paracetamol during pregnancy was associated with communication problems (OR: 1.38, 95% CI 0.98-1.95) and delayed motor milestone attainment (OR: 1.35, 95% CI 1.07-1.70). There were no observed increased risks after short-term exposure. Sensitivity analyses for several indications showed similar effects, suggesting no confounding by indication. Strengths of the study include a large sample size with extensive information on medication use, a data set that allowed for control of confounders, including confounding by indication, and the ability to examine a range of outcomes potentially related with neurodevelopmental difficulties. Limitations include a healthy patient population that might reduce generalizability, inability to control for severe infections due to small subgroup samples, exposure misclassification, and the possibility of chance finding (a possibility that is far less likely given the rest of the literature). The study authors ultimately advised that "[c]aution is warranted when considering long-term use of paracetamol during pregnancy."

Liew et al. (2016),[184] found that maternal acetaminophen use during pregnancy was associated with lower performance IQ in 5-year-olds. The authors noted that their study "adds to the accumulating evidence that acetaminophen exposure in utero alters neurodevelopment in the offspring." The study investigated 1,491 mothers and children enrolled in the Danish National Birth Cohort (DNBC; 1996-2002). Children's IQ was assessed at age 5 with the Wechsler Primary and Preschool Scales of Intelligence-Revised (WPPSI-R). Children born to mothers using acetaminophen without reporting fever scored on average 3.4 points lower (95% confidence interval [CI]: 0.30 to 6.6 points) on performance IQ compared with offspring of mothers who neither experienced fever nor took acetaminophen. Estimated effects for acetaminophen were stronger for first or second trimester use. Children born to mothers reporting fever without using acetaminophen also scored lower on verbal (2.7 points, 95% CI: -0.19, 5.6) and performance IQ (4.3 points, 95% CI: 0.30, 8.3); IQ scores were not affected if mothers with fever used acetaminophen. Strengths of the study include the ability to control for a wide variety of confounders—in particular maternal IQ, parental education levels, and correlates with acetaminophen use—as well as a large sample size, and the use of trained psychologists to administer the IQ tests. Limitations include the theoretical possibility of uncontrolled confounding, certain data limitations on maternal migraine and triptan exposures, and variability in measurement of IQ in young children.

Skovlund et al. (2017),[185] investigated the Norwegian Mother and Child Cohort Study aimed to determine if there was an association between prenatal exposure to analgesic opioids and language competence and communication skills at 3 years of age. The paper also reported information on the

associations with acetaminophen. A total of 45,211 women with 51,679 singleton pregnancies were included, and 892 pregnancies (1.7%) reported the use of analgesic opioids. Use of paracetamol were associated with a small reduction in communication skills, but not language competence.

Bornehag et al. (2018),[20] found that "prenatal acetaminophen use was significantly associated with language delay in girls but not boys," at 30 months of age. The study was conducted in the Swedish Environmental Longitudinal Mother and child, Asthma and allergy (SELMA) cohort. The study relied on maternal self-reports of acetaminophen exposure, and women who responded that they had taken acetaminophen were asked to estimate the number of tablets they had taken. Urine samples were also gathered and urinary acetaminophen concentrations were measured in a subset of women. As the authors noted, "these results are consistent with studies that have examined acetaminophen in relation to IQ and communication problems," *i.e.*, consistent with the Liew (2016), Brandlistuen, and Vlenterie studies described above. Strengths of the study include a prospective design, the use of controls for a number of potential confounders, and the measurement of an instrument (language delay at 30 months) that "is assessed uniformly at all 30-month clinic visits in Sweden" and "has been shown to be predictive of neuropsychiatric and neurodevelopmental outcomes in children." Limitations include the potential for exposure misclassification, the potential for outcome misclassification, and the theoretical possibility of unmeasured confounding, though the authors believed this was an "unlikely" explanation for their findings. The study authors specifically noted that their data "do not support confounding by indication," because the results did not change even when the model controlled for the mother's number of colds and use of antibiotics and other medications—and the fact that it is unlikely that every indication for acetaminophen "would be linked to language delay." The authors concluded that if their findings were replicated, they would "suggest that pregnant women take the precautionary action of limiting their use of" acetaminophen.

Ruisch et al. (2018),[186] prospectively studied a broad range of pregnancy factors in relation to both offspring oppositional-defiant disorder (ODD) and conduct disorder (CD) symptoms in the Avon Longitudinal Study of Parent and Children. Outcomes were ODD and CD symptom scores at age 7 and 9 years using the Development and Well-Being Assessment interview. The authors analyzed maternal (N ≈ 6300) and teacher ratings (N ≈ 4400). The study showed that that higher ODD symptom scores in children at age 7 and 9 years were linked to maternal use of acetaminophen (IRR = 1.24 [98.3% confidence interval 1.05-1.47], P = 0.002, teacher ratings) during pregnancy.

Laue et al. (2019),[3] on which I was a co-author, investigated the association between in utero exposure to acetaminophen and neurodevelopment using concentrations of acetaminophen measured in meconium in 118 children. Women were recruited in Sherbrooke, Canada between 2007 and 2009 during the first trimester of pregnancy and at delivery. Children were evaluated at age 6-8 years using the Wechsler Intelligence Scale for Children (WISC-IV). The study detected acetaminophen in 53% of the study population's meconium samples. In fully adjusted models, there was no statistically significant association between in utero exposure to acetaminophen and decreased scores on any of the examined WISC-IV domains. Strengths of the study include its use of meconium to directly measure acetaminophen levels and its prospective design. Limitations include its small sample size, inability to control for indication, the possibility of residual confounding, and an outcome—intelligence score—that does not directly bear on ADHD or ASD. Indeed, the authors noted that while these results are "discordant" with some of the studies reviewed above—because it showed a null result—the results "are not necessarily in conflict." As the authors noted, "behavior and intelligence are different neuropsychological constructs," meaning that the *Laue* results "cannot be directly compared with other studies."

Tovo-Rodrigues et al. (2020),[187] could "not confirm the existence of a risk effect of acetaminophen used during pregnancy on offspring low neurodevelopmental performance at 24 months and emotional/behavioural problems at 48 months of life"—a result that the authors acknowledge was "in contrast to previous reports of confirmed risk in the literature." The study examined the association between prenatal exposure to acetaminophen and neurodevelopmental performance at 24 months, as well as behavioural and emotional problems at 48 months. Data from the 2004 Pelotas Birth Cohort was used, with 3,737 participants for the neurodevelopmental assessment at 24 months, and 3,624 for the behavioral/emotional assessment at 48 months. Acetaminophen use during pregnancy was not found to be associated with low neurodevelopmental performance at 24 months or emotional/behavioral problems at 48 months in the adjusted models. Strengths of the study include a relatively large data set from Brazil, a high follow-up rate, and adjustment for a variety of potential confounders. But this study had serious limitations, likely explaining its different result. Data on medication use was gathered retrospectively, "which may have resulted in difficulty recalling acetaminophen use." The study was not able to address dose response. And the low acetaminophen usage rates resulted in the study being underpowered, leading the authors to candidly admit that they "expect that the effect sizes observed in the association analysis were underestimated."

Bertoldi et al. (2020),[187] examined the associations of prenatal and early-life exposure to acetaminophen with cognitive, motor, and language skills in children from two birth cohorts. The American Project Viva cohort (1217 mother-child pairs) and the Brazilian 2015 Pelotas Birth Cohort (3818 mother-child pairs) assessed cognition in children at approximately 3 years and 2 years, respectively. Linear regression was used to estimate the associations of acetaminophen use during pregnancy (Project Viva and Pelotas) and infancy (Project Viva) with children's cognitive scores adjusted for several confounding variables. In Project Viva, exposure to acetaminophen in both the 1st and 2nd trimester of pregnancy was associated with lower drawing scores (β -1.51, 95% CI -2.92, -0.10) on the Peabody Picture Vocabulary Test and the Wide Range Achievement of Visual Motor Abilities test. However, in Pelotas, exposure to acetaminophen in both the 1st and 2nd trimester of pregnancy was not associated with INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA) motor scores (β 0.02; 95% CI -0.05, 0.09) and was associated with higher INTER-NDA total scores (β 0.08, 95% CI 0.01, 0.16). Other comparisons did not show evidence for any associations. Strengths of the study include use of tests that measured cognition and motor function, allowing examination of aspects of neurodevelopment that had not been previously studied in detail. But the limitations were severe. The authors used different tests (at different ages) to measure outcomes in the two cohorts, there was no information about dose, there was a likelihood of underreporting in the self-reported questionnaires, and there was the possibility of confounding by indication. This study did not add materially to the existing literature, as the authors acknowledged, stating that "[i]nconsistencies and lack of specificity of the findings did not clarify the research question considering that we still have a large variability and uncertainty to define the risk or safety in the use of acetaminophen related to cognition in early childhood."

Parker et al. (2020),[188] found that "acetaminophen use during pregnancy was weakly associated with mother-reported behaviour problems and not associated with teacher-reported problems." The study assessed the association between maternal acetaminophen use during pregnancy and behavior problems in childhood based on mother and teacher reports. A longitudinal study of 560 mother-child pairs with data on illnesses and medication use during pregnancy and neurodevelopmental assessments during childhood was conducted. Approximately 60% of women reported use of acetaminophen during pregnancy. The results showed that acetaminophen use during pregnancy was associated with an increase in total behavior problem score and risk of clinical behavior problems according to mother report but not according to teacher report. The adjusted mean difference was 2.2 (95% CI 0.3, 4.1) and the risk ratio was 1.93 (95% CI 0.99, 3.76) for mother report. However, adjustment for indications of acetaminophen use greatly attenuated the associations with mother-reported total behavior problem

score and risk of clinical behavior problems. Strengths of the study include weighting to account for loss to follow-up, the ability to adjust for many potential confounders, including fever and inflammation, and detailed exposure assessment. Limitations include exposure data collected in retrospective, self-reported manner, the possibility of misclassification given the absence of an association in the teacher-reported outcomes, and the absence of data on some potential confounders.

Rifas-Shiman et al. (2020),[189] found that prenatal exposure to acetaminophen was "associated with poorer executive function and behaviour in childhood." The authors noted that these results are "consistent with previous studies that reported associations of acetaminophen in pregnancy with greater childhood executive function and behaviour problems." The study examined the association between prenatal exposure to acetaminophen and ibuprofen and neurobehavioral problems in children. The study included 1225 mother-child pairs from Project Viva, a pre-birth cohort study. The mothers completed questionnaires on prenatal acetaminophen and ibuprofen use in early and mid-pregnancy. Parents and classroom teachers assessed child behaviors in mid-childhood (median 8 years) using the Behavior Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ). Higher (≥10 vs <10 times) prenatal acetaminophen (β 1.64 points; 95% confidence interval [CI] 0.59, 2.68) and any ibuprofen (β 1.56, 95% CI 0.19, 2.92) were associated with higher parent-rated BRIEF global scores. Patterns of association were linear across categories and were similar for other parent- and teacher-rated outcomes. Strengths of the study include prospective data collection, assessment of exposure at multiple timepoints, adjustment for many confounders, and a relatively large sample size. Limitations include lack of precise dose data, the possibility of exposure through lactation, and the theoretical possibility of unmeasured confounding—although the authors specifically noted that "the strong and consistent associations and lack of any notable attenuation with adjustment for measured confounders render it less likely that the observed relationship is entirely explained by unmeasured confounding." The study authors concluded that these findings highlight the need for further research on the mechanisms through which analgesics may act on fetal and child brain development.

Golding et al. (2020),[190] aimed to determine if paracetamol (acetaminophen) intake between 18 to 32 weeks gestation is associated with childhood behavioral and cognitive outcomes. The study used data collected by the Avon Longitudinal Study of Parents and Children (ALSPAC) and identified that 43.9% of women took paracetamol during pregnancy. The study identified 12 outcomes showing independent associations with paracetamol use in mid-to-late pregnancy, primarily related to child's behavior reported by the mother at 42 and 47 months, such as conduct problems. Few associations were found

with behavioral or neurocognitive outcomes after age 7-8 years, whether reported by the mother or teacher. Strengths of this study include a geographically defined population of women selected for reasons unrelated to exposure or outcome and information collected from a variety of data sources—including hands-on assessments and questionnaires from parents and teachers. Limitations include very limited ability to adjust for confounding, small sample size, and evaluation of acetaminophen use only between 18 and 32 weeks (and not later or earlier in pregnancy).

Tronnes et al. (2020),[191] found "an association between paracetamol use in multiple trimesters and lower shyness – and greater internalizing behaviour in preschool-aged children." The study investigated the potential association between duration and timing of prenatal paracetamol exposure and neurodevelopmental outcomes in children. Data was obtained from the Norwegian Mother and Child Cohort Study. Of the 32,934 children included in the study, 25.4%, 15.1%, and 5.4% were prenatally exposed to paracetamol in one, two, and three trimesters, respectively. Children exposed to paracetamol in two trimesters scored lower on shyness compared with unexposed children (β -0.62, 95% confidence interval [CI] -1.05, -0.19). Children exposed to paracetamol in three trimesters had a moderate increased risk of internalizing behavior problems (relative risk (RR) 1.36, 95% CI 1.02, 1.80) and borderline externalizing behavior problems (RR 1.22, 95% CI 0.93, 1.60) compared with unexposed children. Children exposed to paracetamol in 2nd/3rd trimester scored lower on shyness (β -0.32, 95% CI -0.66, 0.02) compared with unexposed children. Strengths of the study include its large sample size, prospective design, and long follow up. The data set was a rich and detailed one, allowing for the measurement control of a variety of confounders, including indication. Limitations include a relatively low participation rate, the possibility of non-differential exposure misclassification, and the inability to measure dose directly, requiring the number of days of use to be used as a proxy.

Inoue et al. (2021),[192] "corroborates published associations between prenatal exposures to acetaminophen and behavioral problems," including in "early adolescence." The study evaluated the associations between prenatal and postnatal exposure to acetaminophen and behavioral problems in children at the age of 11 years. They used behavioral measures reported by both parents and children and studied 40,934 mother-child pairs from the Danish National Birth Cohort enrolled during 1996-2002. The parent-reported and child-reported Strengths and Difficulties Questionnaire (SDQ) responses were collected during the 11-year follow-up. The results showed that prenatal acetaminophen exposure was associated with 10%-40% higher risks for total difficulties and internalizing and externalizing problems based on parent- or child-reported SDQ. The association was stronger for greater cumulative weeks of

acetaminophen use. Postnatal exposure was associated with 16%-19% higher risks for parent-reported internalizing behaviors, but the associations were weak or null for child-reported scores except for prosocial behavior. Overall, in this study, "maternal acetaminophen use during pregnancy was consistently associated with increased risks for offspring developing behavioral and emotional problems at 11 years of age, using outcome measures reported by the parent or the child," results that the authors described as "consistent." Strengths of this study include its large cohort design, with sample sizes providing substantial power, its use of multiple informants in outcome assessments, and repeated assessment of prenatal acetaminophen use. Limitations include the use of self-reporting for both exposure and outcome variables, no direct data on dosage of pills taken, and the theoretical possibility of unmeasured confounding.

4. Special Techniques Used to Assess Unmeasured and Genetic Confounding in Investigations of the Association of Prenatal Acetaminophen with ADHD, ASD, and other Neurodevelopmental Disorders

Observational studies play a crucial role in studying the safety of medications during pregnancy. However, observational studies need to accurately assess and control for confounding, which can otherwise affect the accuracy of the findings. To overcome this challenge, researchers typically use data analysis methods like stratification, multivariable analysis and propensity score calibrations. These methods help to control for complex confounding variables that are measured in the study. As detailed above and in the underlying studies, the literature on acetaminophen and ADHD controls for a wide variety of potential confounders—from maternal illness to socioeconomic status to indication of use—and yet the association has persisted despite the controls. This alone is powerful evidence that the observed association is causal rather than the result of confounding.

That said, these statistical methods might not always be able to completely account for confounding factors that are unmeasured or unknown. Even so, this theoretical possibility of unmeasured confounders must not be overstated. Bradford Hill cautioned against rejecting a causal inference just because of the possibility of unmeasured confounders, noting that "if we cannot detect it or reasonably infer a specific one," then this possibility amounts to "the vague contention of the armchair critic 'you can't prove it, there *may* be such a feature.'"[2] Nevertheless, to explore the possibility of residual and unmeasured confounding, novel techniques have more recently been developed and applied, including negative control exposures, sibling-controlled analysis, and polygenic risk scores for the specific case of unmeasured genetic confounders. It is important to note that these designs have been used in the

literature to address concerns related to unmeasured confounding in acetaminophen-ADHD studies, including confounding by indication and genetic-family factors. This section reviews the advantages and limitations of these approaches and their use in the investigation of the association between prenatal acetaminophen use and NDDs. The use of these novel techniques—which attempt to control for the effects of unmeasurable or residual confounding—provide even more compelling evidence that the association here is a real, causal one.

a. Negative Control Exposures (NCE) to Adjust for Unmeasured Confounding.

"The approach of examining associations with other outcomes (or other exposures) that should have no causal effects is sometimes referred to as one of using 'negative controls."[5] Negative control exposures are a valuable tool in research studies for assessing the influence of unmeasured or unknown confounding factors when investigating associations between a specific exposure and an outcome of interest. Similar to negative controls in laboratory science, negative control exposures serve the purpose of evaluating the specific effects of the exposure by ensuring that observed outcomes are not influenced by unrelated factors. Negative control exposures are variables that are not biologically or theoretically related to the outcome under investigation but share the same confounding structure with the exposure of interest. By examining the association between a negative control exposure and the outcome, researchers can determine if unmeasured confounding factors are potentially impacting the results. If a negative control exposure shows no association with the outcome, it provides reassurance against biased results from unmeasured confounders. By employing negative control exposures, researchers can provide additional evidence to support the validity of their findings and increase confidence in the association between prenatal acetaminophen use and NDDs.

In the context of the association between prenatal acetaminophen and NDDs, negative control exposures have been used in four studies, *i.e.*, Liew et al. (2019)[13], Stergiakouli et al. (2016)[13], Ystrom et al. (2017)[11], and Tronnes et al. (2020)[191].

Liew et al. (2019),[12] presented a negative control exposure analysis that examined the associations between different exposure periods of acetaminophen use and childhood ADHD in the Nurses' Health Study II cohort, a study that I have already reviewed in section G.1.a. In this cohort, information about the participants' use of acetaminophen was collected prospectively every two years. Regular maternal acetaminophen use (yes/no) reported on the questionnaire during the year of the child's birth was

analyzed as the index exposure variable of interest and referred to "regular acetaminophen use at the time of pregnancy."

The authors used two negative control exposure variables – specifically, the authors used the same maternal regular use variables from the questionnaires completed two cycles (*i.e.*, 4 years) before and after the one completed at the time of pregnancy. In other words, the authors looked at acetaminophen use *before* and *after* pregnancy. According to the authors, these exposure periods make good NCE variables. The authors noted that these variables would not affect the offspring's risks of ADHD in a pregnancy four years before or later and that time-invariant variables that could have introduced confounding in other studies—such as genetic factors, maternal chronic illnesses, family and social factors, and/or general medication use behaviors and choices—would affect these other exposure periods in the same way as they would during the pregnancy.

The analysis suggested that *only* acetaminophen use at the time of pregnancy was associated with childhood ADHD (OR = 1.34, 95% CI: 1.05, 1.72), while the effect estimates for the two negative control exposure periods were null (OR = 1.06, 95% CI 1.06-1.38 for use of acetaminophen 4 years before the pregnancy and OR = 0.97; 95% CI 0.80-1.18 for use of acetaminophen after the pregnancy). This suggests that the paper's overall results are not due to unmeasured confounding, because only acetaminophen use *during* pregnancy was associated with ADHD. As the authors put it, "the findings of our NCE analyses corroborate those of prior reports suggesting that prenatal acetaminophen exposure may influence neurodevelopment."

The paper's main findings remained consistent across various sensitivity analyses. The positive association between acetaminophen use during pregnancy and ADHD in children was largely unaffected when the authors examined subgroups of mothers without depression, rheumatoid arthritis, or migraine headache, and when they excluded mothers who used aspirin and other nonsteroidal anti-inflammatory drugs during pregnancy. Although the estimates became slightly less precise, the magnitude of the associations remained unchanged when they adjusted for additional maternal social demographic and lifestyle factors. Furthermore, using a tighter definition of exposure to acetaminophen (*i.e.*, identifying as exposed only mothers who confirmed to be pregnant at the time of the interview) moderately strengthened the effect estimates.

These findings support prior evidence suggesting a link between prenatal acetaminophen exposure and neurodevelopmental effects, while also providing assurance that uncontrolled factors unrelated to the exposure do not explain this association.

Stergiakouli et al. (2016),[13] investigated the associations between offspring behavioral problems and maternal prenatal acetaminophen use during pregnancy in a large prospective birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK. The authors used (a) the partner's acetaminophen use, and (b) maternal acetaminophen use after pregnancy as negative control exposures to account for unmeasured and familial confounding. If an intrauterine effect of acetaminophen exposure on offspring behavior is present—*i.e.*, if prenatal acetaminophen exposure really does cause ADHD and ASD—one would expect association with maternal prenatal exposure but not with maternal postnatal exposure or partner's exposure because only the maternal prenatal exposure has direct biological effect on the fetus.

The results showed that maternal prenatal acetaminophen use at 18 weeks of pregnancy was associated with an increased risk of conduct problems (RR = 1.42; 95% CI, 1.25-1.62) and hyperactivity symptoms (RR = 1.31; 95% CI, 1.16-1.49) in children. Maternal acetaminophen use at 36 weeks of pregnancy was associated with emotional symptoms (RR = 1.29; 95% CI, 1.09-1.53), and overall difficulties in children (RR = 1.46; 95% CI, 1.21-1.77). No associations were observed for maternal postnatal or partner's acetaminophen use.

Based on these results, the authors concluded that their findings "suggest that the association between prenatal acetaminophen exposure and childhood behavioral problems is not explained by unmeasured familial factors linked to both acetaminophen use and childhood behavioral problems and that the findings are consistent with an intrauterine effect," *i.e.*, consistent with prenatal acetaminophen exposure causing these behavioral problems.

In Ystrom 2017,[11] described in detail above, in addition to the primary analysis, the authors also evaluated whether maternal pre-conceptional use was associated with ADHD, *i.e.*, whether mothers who took acetaminophen *before* they became pregnant (but not *while* pregnant) were at a higher risk of having children with ADHD. They determined that "[m]aternal preconceptional use was not associated with ADHD," a result that they described as "in line with" the Stergiakouli study described above. In other words, even though mothers who took acetaminophen *while* pregnant were at a greater risk of having children with ADHD, mothers who took acetaminophen *before* becoming pregnant were not

suggesting that the use of the acetaminophen (rather than some feature of mothers who tend to take acetaminophen) is driving the association. This result further bolsters the case for causation (and the case against residual confounding being the explanation for the observed association). Indeed, as the authors noted specifically, this result is "consistent with a causal link."

Another study, Tronnes et al. (2020),[191] and one analysis in Ystrom et al. (2017),[11] showed potentially conflicting results.

As noted above, in Ystrom et al. (2017),[11] paternal use of acetaminophen (for 29 days or more) was associated with ADHD (HR = 2.06 CI, 1.36-3.13). Although the authors noted that this result provided reason to question "the causal role of acetaminophen," there is nothing inconsistent with causation, as even the authors recognized. Specifically, they noted that "[t]he mechanics of the ADHD effect of paternal acetaminophen use before pregnancy are unclear" but "it may be due to male germ-line epigenetic effects as described in endocrine disruption effects of acetaminophen on the human testis." In other words, they proposed a causal interpretation even for the paternal-acetaminophen-use result. Meanwhile, as the authors noted, "Paternal use was associated with maternal preconceptional use and use during pregnancy (r = 0.18–0.10)"—unsurprising, given that fathers and mothers often share medications and medicine cabinets—which means paternal use might have been serving as an imperfect proxy for *maternal* use, rather than serving as a valid negative control.

In Tronnes et al. (2020),[191] the authors' primary finding was that there was an increased risk of "internalizing behavior" and "externalizing behavior" in "children exposed to [acetaminophen] in three trimesters compared with unexposed children."[191] The authors also performed a negative control analysis of women who used acetaminophen "prior to pregnancy only." The children of these women showed a barely statistically significant increase in communication problems and activity levels. The authors suggested that this might indicate some unmeasured confounding in the observed associations that could have played some role. That said, I did not view this negative control analysis as persuasive. The Tronnes study did not have ADHD as an endpoint and was forced to rely on less clearly defined child outcomes. And the negative control group showed "different outcomes than those identified in the main analysis," *i.e.*, children of mothers who took acetaminophen prior to pregnancy did *not* exhibit the same behavioral issues that children of mothers who took acetaminophen during pregnancy.

Given the strengths and weaknesses of the negative control analyses described above, my opinion is that on balance they dramatically strengthen the inference that the observed association between acetaminophen and ADHD is causal rather than the result of theoretical, unmeasured confounding.

b. Sibling-Controlled Design.

To further address the concern that the reported associations between maternal use of acetaminophen in pregnancy and child's neurodevelopmental outcomes may be caused by unmeasured confounding factors, some studies have employed a sibling-controlled design, whereby pairs of matched siblings are used to further control for unmeasured confounding.

In Brandlistuen et al. (2013),[14] "[i]n the sibling-control analysis, prenatal paracetamol exposure for 28 days was associated with poor gross motor functioning, delayed age starting to walk, poor communication skills, externalizing and internalizing behaviour problems and an active temperament." In other words, as compared to the sibling *not* exposed to acetaminophen in utero, the sibling who *was* exposed displayed more of these markers of NDDs. As the authors noted, "[t]he sibling-control design represents a more conservative step toward control for potential selection bias than conventional covariate adjustment because stable selection factors (*e.g.* socio-economic status) are completely adjusted for in the sibling-control design." In other words, these results provide greater comfort that unmeasured, residual confounding is not driving the association between acetaminophen and ADHD.

Gustavson et al. (2021)[173] also proposed to use a sibling control design in a study of prenatal acetaminophen and child's ADHD. The authors proposed the sibling control design to assess the confounding effect of maternal/familial factors, including genetics, that may increase the risk of mothers using acetaminophen during pregnancy and also affect the child's neurodevelopment.

The authors proposed that sibling control studies, wherein the risk of ADHD is compared between two differently exposed siblings, may help assess potential familial confounding of the association between prenatal acetaminophen exposure and ADHD. They suggested that if there is a causal effect, the exposed sibling is expected to have a higher risk of developing ADHD than the unexposed sibling. If the association is mainly explained by familial confounding factors, the ADHD risk should be similar for the two siblings.

The authors performed a standard analysis and a sibling-control analysis side-to-side on data from the prospective Norwegian Mother, Father, and Child Cohort Study (MoBa) cohort study. The results of the

association between prenatal acetaminophen and ADHD in MoBa had been previously published in Ystrom et al. (2017), which I reviewed in Section G.1. Similar to the findings in the latter paper, Gustavson et al. (2021),[173] reported that long-term exposure (29 days or more) to prenatal acetaminophen was associated with a two-fold increase in risk of ADHD diagnosis (adjusted HR = 2.02, 95% C.I = 1.17–3.25) in a standard analysis. In the sibling control model, the association between long-term acetaminophen use and ADHD in the child was adjusted HR = 2.77 (95% C.I. = 1.48–5.05) at the between-family level, and adjusted HR = 1.06 (95% C.I. = 0.51–2.05) at the within-family level. Based on these findings, the authors concluded that the analysis revealed a "substantial family effect" that "suggested that unmeasured familial confounding factors may explain at least part of the observed association between maternal long-term acetaminophen use and ADHD in the child".

Unfortunately, Gustavson et al. (2021), did not sufficiently explain how the family effect identified by their sibling-control design may have impacted the association between prenatal acetaminophen and child's ADHD. Indeed, Sjölander et al. (2017),[193] showed that the sibling-control design eliminates not only the impact of family factors that operate as confounders but also that of family factors that operate as mediators. While controlling for confounders is desirable, controlling for mediators would cause bias when investigating whether prenatal acetaminophen is a causal factor for the child's ADHD. The Gustavson authors explicitly admit that this was likely a problem with their analysis, stating that the "sibling comparison model adjusts not only for stable confounding factors, but also for potential mediating factors that affect all siblings even if only one is exposed." As they note, "this may lead to underestimation of association estimates."

Here below, I define the concept of "mediation" in epidemiology studies and then review how controlling for a mediator is undesirable.

c. The Concept of "Mediators" in Epidemiology

In epidemiology, a mediator is a variable that lies along the causal pathway between an exposure and an outcome. It helps to explain or mediate the relationship between the exposure and the outcome by providing insight into the underlying mechanisms or processes through which the exposure influences the outcome. A mediator variable is influenced by the exposure and, in turn, influences the outcome. It represents an intermediate step or factor that helps to transmit the effects of the exposure to the outcome. The presence or absence of mediation can help elucidate the causal pathways and shed light

on the underlying biological, behavioral, or social processes involved in the relationship between the exposure and the outcome.

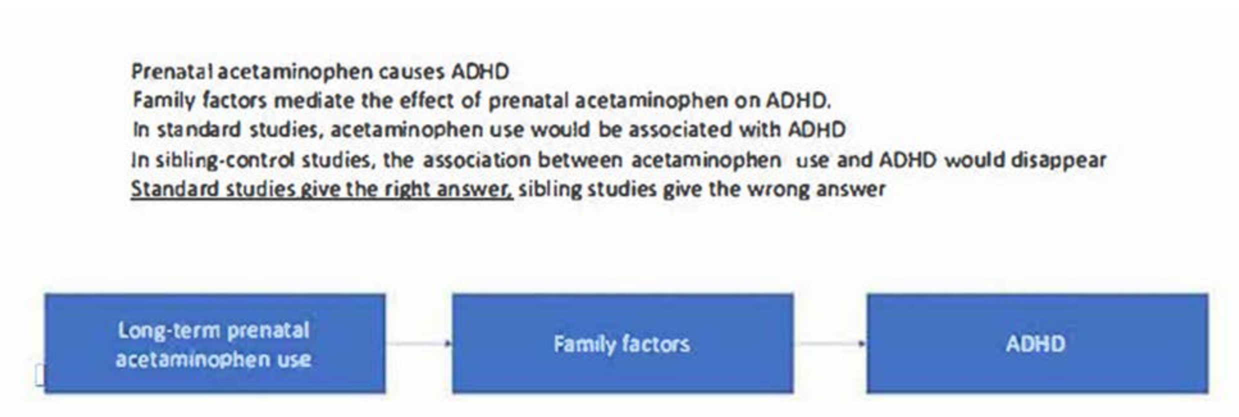
In the context of the association between prenatal acetaminophen exposure and ADHD (Attention-Deficit/Hyperactivity Disorder), a mediator refers to a variable or mechanism that helps explain how or why prenatal acetaminophen exposure might lead to the development of ADHD symptoms in children. In the case of family-related effects that are controlled through a sibling-control analysis, a potential mediator could be a family-driven biological, genetic, psychological, or behavioral process that is influenced by prenatal acetaminophen exposure and subsequently contributes to the development of ADHD.

When addressing the question of whether prenatal acetaminophen is causally associated with ADHD, epidemiologists need to avoid controlling for mediators. Doing so would cause true associations to disappear, *i.e.*, controlling by intermediates would cause bias.

d. The Impact of a Sibling-Control Analysis on a Study of Prenatal Acetaminophen Use and child ADHD

To explain how sibling-control analysis may generate misleading results, I present two scenarios showing how controlling for mediators improperly conceals a true association between prenatal acetaminophen and ADHD. I also present a second scenario that reviews how adjusting for a variable that controls a mediator (often included in the broader concept of effect modifier) would bias the results.

Scenario #1 -- Mediation.



In Scenario #1, we are examining mediation in the association between prenatal acetaminophen use and ADHD. Mediation refers to a situation where an intermediate factor (mediator) plays a role in the causal pathway between an exposure and an outcome.

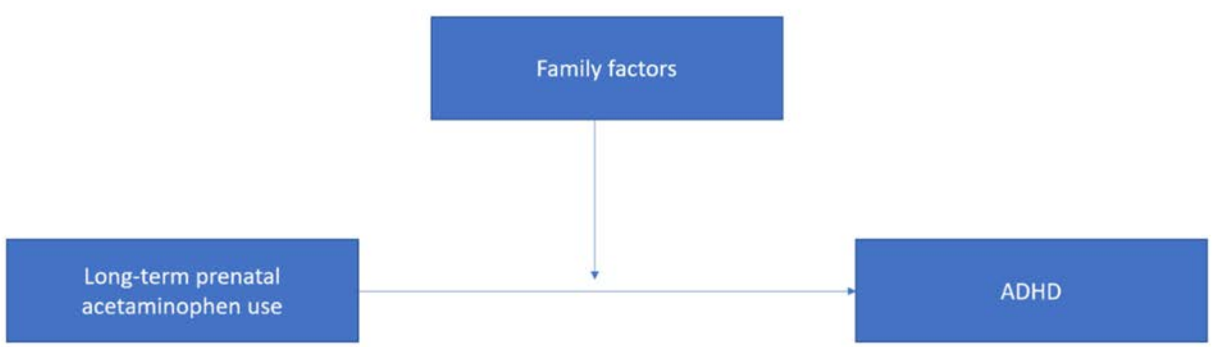
In this scenario, it is hypothesized that prenatal acetaminophen use is the cause of ADHD, and family factors mediate the effect of acetaminophen on ADHD. Family factors, in this case, act as an intermediate step through which the effect of prenatal acetaminophen on ADHD is transmitted.

Standard studies (that do not control for mediators, as widely recommended to estimate the overall effect of an exposure on an outcome) would reveal the association between prenatal acetaminophen use and ADHD. However, when sibling-control studies are conducted, the association between acetaminophen use and ADHD would disappear.

The sibling-control studies, in this scenario, give the wrong answer by not showing the association between acetaminophen use and ADHD. This is because sibling-control studies also take away the mediating role of family factors. On the other hand, the standard studies without sibling control give the right answer by capturing the association between prenatal acetaminophen use and ADHD without taking into account the mediation effect of family factors.

Scenario #2 - Effect Modification

Prenatal acetaminophen causes ADHD
Family factors make the effect of acetaminophen stronger.
In standard studies, acetaminophen use would be associated with ADHD
In sibling-control studies, the association between acetaminophen use and ADHD would disappear
Standard studies give the rigtht answer, sibling studies give the wrong answer



In Scenario #2, we are exploring the concept of effect modification in the association between prenatal acetaminophen use and ADHD. Effect modification occurs when the relationship between an exposure

and an outcome is modified by the presence of another factor. In this scenario, it is hypothesized that prenatal acetaminophen use is the cause of ADHD, and family factors act as effect modifiers, making the effect of acetaminophen stronger in the presence of these factors.

In standard studies, an association between prenatal acetaminophen use and ADHD would be observed. This suggests that acetaminophen use is associated with an increased risk of ADHD, regardless of the presence or absence of family factors.

However, in sibling-control studies, the association between acetaminophen use and ADHD would disappear. This is because sibling-control studies also adjust for family-effects that operate as effect modifiers. Indeed, this situation is akin to adjusting for the main effect of an effect modifier while omitting the interaction terms in a traditional multivariable regression model. *Lefebvre and Gustavson 2020*[194] have shown that this situation causes bias, particularly when—as in the case at hand—the effect modifier is not independent of the exposure of concern.

Hence, in this scenario, sibling-control studies give the wrong answer by not revealing the association between acetaminophen use and ADHD. On the other hand, the standard studies without sibling control would give the right answer by capturing the association between prenatal acetaminophen use and ADHD, even without considering the modifying effect of family factors.

e. Challenges in the Interpretation of Sibling-Control Studies

As indicated above, sibling-control studies of prenatal acetaminophen and child's NDDs would provide incorrect results in two plausible scenarios. Therefore, sibling-control studies are likely to produce artificially low risk estimates when determining whether the associations between prenatal acetaminophen and child's NDDs may be caused by unmeasured and/or unknown confounders.

Particularly, experimental studies have identified many biological mediators of the effects of prenatal acetaminophen on ADHD (See Section E), including increased oxidative stress, alterations of the prostaglandin system, alterations of the cannabinoid system, alterations of the brain-derived neurotrophic factor, endocrine effects, and epigenetic effects. All these mediators show familial aggregation, defined as the tendency for certain traits or conditions to cluster within families. Therefore, individuals within a family are more likely to have higher oxidative stress, alterations of the prostaglandin system, alterations of the cannabinoid system, alterations of brain-derived neurotrophic factor, and similar epigenetics compared to individuals in the general population.

Effect modification by family effects is equally likely in the case of prenatal acetaminophen and NDDs. For instance, genetic variants have been identified that modify the risk, severity of symptoms, and outcome of paracetamol-induced acute liver failure. Several genes, including UGT1A, CD44, CYP3A5, GST-P1, GST-T1, KRT8, and TLA, have been associated with paracetamol-induced acute liver failure. Several of these genes code for proteins that operate in the absorption, distribution, metabolism, and excretion of acetaminophen. Genetic variation (which aggregate within families) of these genes modify the speed of acetaminophen absorption, distribution, metabolism, and excretion in the human body. Therefore, there is plenty of evidence supporting the existence of family-based effect modifiers. The use of a sibling-control design would mistakenly adjust for these unmeasured effect modifiers and lead to incorrect conclusions.

In summary, sibling-control studies have heavy limitations that are likely to lead to misleadingly low estimates of the true risk. These studies have inherent constraints that restrict their ability to appropriately model mediators and effect modifiers.

f. Evaluating Genetics as a Potential Confounder.

Some authors have suggested that the association between maternally influenced prenatal acetaminophen use and child's NDDs may be affected by genetic confounding, whereby an exposure (*i.e.*, acetaminophen use) and a disease (*i.e.*, NDDs) have shared genetic influences. In this case, the genetic makeup of a mother would make her more likely to use acetaminophen and also increase her child's risk of an NDD.

This type of confounding has been thoroughly discussed in relation to ADHD. As for other types of confounding, the genetic factors must be associated with maternal acetaminophen use and the child's ADHD risk. Leppert et al. (2019),[172] built risk scores based on maternal genes (referred to using the technical term "polygenic risk scores") for child's ADHD, ASD, or schizophrenia using the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK. In ALSPAC, the polygenic risk score for ADHD was also associated with maternal acetaminophen use. Having a polygenic score at high risk for ADHD was associated with 9% increased odds of using acetaminophen in early pregnancy (OR = 1.09, 95% CI 1.02-1.17) and 11% increased odds of using acetaminophen in late pregnancy (OR = 1.11, 95% CI 1.04-1.18). The polygenic risk scores for ASD and schizophrenia were not associated with maternal use of acetaminophen during pregnancy.

A separate study on the same cohort addressed this issue. Stergiakouli et al. (2016) (also reviewed above in Section G.3.a.) investigated the association between prenatal acetaminophen and child's ADHD; they found a significant association that was not modified by adjusting for the ADHD polygenic risk score. Taken together, these two papers from the ALSPAC cohort indicate that genetic confounding cannot explain the association between prenatal acetaminophen use and child's ADHD.

It is important to note that multiple other studies have addressed this concern by using maternal family history of neurodevelopmental disease as a proxy of genetic confounding. None of those studies provided evidence suggesting that genetics/maternal familial disease history explain the associations between prenatal acetaminophen and ADHD or ASD.

In addition to evidence from the data reported above, there are a number of theoretical reasons indicating that genetic confounding is unlikely to bias the results. Let us first assume that the association between maternal ADHD polygenic risk scores and prenatal use of acetaminophen is causal, *i.e.*, maternal genetics causes mothers to be slightly more likely to use acetaminophen during pregnancy. In this situation, while maternal genes might be contributing to the likelihood of using acetaminophen during pregnancy, they are not the cause of child's ADHD—the maternal use of acetaminophen during pregnancy is. If we assumed that the association between the ADHD polygenic scores and maternal acetaminophen use is not causal, then any possible confounding would be caused by other variables correlated with genetics, such as for instance race or ethnicity, which have been typically controlled for in most studies investigating prenatal acetaminophen and child's ADHD.

Considering the empirical evidence and theoretical considerations, genetic confounding is unlikely to meaningfully influence the observed association between prenatal acetaminophen use and child's NDDs.

g. Summary of the Evidence from Special Techniques to Evaluate Unmeasured and Genetics Confounding

In summary, the information discussed above provides insights into the evaluation of unmeasured and genetic confounding in the association between prenatal acetaminophen use and NDDs. Highly sophisticated epidemiology techniques have been employed to address these confounding factors, and the overall findings do not suggest that the observed associations are attributable to unaccounted confounding.

Negative control exposure studies, which aim to identify unmeasured confounding, have been conducted and did not find compelling evidence of significant confounding in the association between prenatal acetaminophen use and NDDs. These studies suggest that factors not accounted for in the analyses are unlikely to explain the observed associations.

Furthermore, data on polygenic risk scores, a measure of genetic predisposition, were examined in relation to prenatal acetaminophen use and ADHD. The findings indicate that genetic factors are unlikely to confound the results in this context.

Lastly, sibling control studies, which are another approach to assess confounding, have produced conflicting results. It is unclear whether these studies provide any meaningful evidence regarding the role of unmeasured or genetic confounding in the association between prenatal acetaminophen use and NDDs.

Overall, based on the information discussed, the available evidence does not suggest that unmeasured confounding or genetic factors account for the observed associations between prenatal acetaminophen use and NDDs.

h. The Interplay Between Fever and Acetaminophen in Relation to Neurodevelopmental Disorders

In this section, I delve into the interplay between fever and prenatal acetaminophen use and its potential impact on the development of neurodevelopmental disorders in children, especially ADHD and autism spectrum disorder ASD.

Studies have linked maternal fever during pregnancy to an increased risk of neurodevelopmental disorders in offspring. Simultaneously, prenatal acetaminophen use, often used in an attempt to alleviate fever symptoms, has been associated with adverse neurodevelopmental outcomes. This prompts me to explore the interplay between fever, prenatal acetaminophen use, and their potential effects on child neurodevelopment.

Within the literature, two types of studies have been conducted to investigate this interplay. Firstly, studies have explored whether the effect of prenatal acetaminophen on neurodevelopmental disorders differs depending on whether it was used specifically to treat fever or for other reasons. By reviewing these studies, I aim to discern whether the possible association between acetaminophen use and

neurodevelopmental disorders is modified by the specific indication of fever or if it is independent of fever.

Secondly, I examine studies that investigated whether the effect of fever on neurodevelopmental disorders is attenuated in individuals who took acetaminophen during fever episodes. By investigating this, I aim to shed light on the potential protective role of acetaminophen in mitigating the adverse effects of fever on neurodevelopment.

By synthesizing findings from both types of studies, I aim to provide an understanding of the interplay between fever, prenatal acetaminophen use, and neurodevelopmental disorders.

i. Studies Investigating Whether the Effects of Acetaminophen on ADHD and ASD Are Modified by Fever

Several studies have investigated whether the effects of acetaminophen on ADHD/ASD differ depending on whether the prenatal use was prompted by fever vs. other indications.

Ystrom et al. (2017), found that "long-term maternal use of acetaminophen during pregnancy is associated with ADHD in offspring," even "after adjusting for potential confounders, including parental symptoms of ADHD and indications of acetaminophen use." The study examined the relationship between maternal and paternal use of acetaminophen and ADHD in offspring, while accounting for familial risk and reasons for acetaminophen use. Diagnoses from the Norwegian Patient Registry were analyzed for 112,973 offspring, of which 2,246 had ADHD. The analysis revealed that any prenatal maternal use of acetaminophen during pregnancy was associated with a 12% increased risk of ADHD (HR = 1.12, 95% CI: 1.02-1.24).

One feature of this study is that it collected detailed information about acetaminophen use, including the total number of days of use. The risk of ADHD increased with the total number of days of acetaminophen use (see table below) providing compelling evidence of dose response. The highest risk of child's ADHD was found in women who reported 29 days or more of use during pregnancy (HR=2.20, 95% CI: 1.50=3.24), indicating a more than doubling of the risk of ADHD, as shown in the table below.

TABLE 2 HRs for Offspring ADHD by Number of Days of Maternal Acetaminophen Use During Pregnancy

	All Indications		Groups of Indications for Acetaminophen Use					
			Fever and Infections		Pain Conditions		Indication Not Specified	
	No. of Mothers Reporting Each Exposure Duration / Overall No. of Observations of Use per Exposure Duration	Adjusted HR* (95% CI)	No. of Mothers Reporting Each Exposure Duration / Overall No. of Observations of Use per Exposure Duration	Adjusted HR* (95% CI)	No. of Mothers Reporting Each Exposure Duration / Overall No. of Observations of Use per Exposure Duration	Adjusted HR* (95% CI)	No. of Mothers Reporting Each Exposure Duration / Overall No. of Observations of Use per Exposure Duration	Adjusted HR* (95% CI)
No use	103017 1 153338	1.00 Reference	84 304 216 206	1.00 Reference	75 019 180288	1.00 Reference	4606 4639	1.00 Reference
1–7 d	36899 53667	0.90 (0.81–1.00)	8752 10 864	0.90 (0.75–1.09)	10 335 12 064	0.89 (0.76–1.04)	19154 21796	1.30 (0.98–1.73)
8–14 d	6434 7923	1.18 (0.98–1.42)	1021 1185	1.02 (0.55–1.89)	2653 2925	1.12 (0.83–1.50)	1949 2020	1.96 (1.36–2.82)
15–21 d	2003 2369	1.35 (1.00–1.81)	185 200	0.98 (0.24–3.95)	1045 1147	1.43 (0.96–2.14)	441 447	1.79 (0.95–3.35)
22–28 d	253 283	1.60 (0.70–3.69)	16 17	6.15 (1.71–22.05)	133 138	1.08 (0.34–3.39)	61 62	—
29 or more d	1034 1395	2.20 (1.50–3.24)	72 75	2.40 (0.34–16.78)	609 772	2.56 (1.54–4.25)	200 212	2.13 (0.88–5.15)

—, not applicable.
* Adjusted for year of birth, maternal age, parity, comedication within each indication of use, acetaminophen use first 6 months before pregnancy within each indication of use (only reports on first trimester are adjusted), and acetaminophen use in the first 6 months postpartum within each indication of use (only reports on last trimester are adjusted). Two thousand two hundred and forty six children were diagnosed with ADHD by December 31, 2014.

The table also shows stratified analysis by indication, by separating fever and infections or pain, as well as unspecified. The HRs for the association between acetaminophen use and were similar across these indications and the confidence intervals are largely overlapping.

Liew et al. (2016),[167] which I also reviewed earlier, presented "evidence that paracetamol use during pregnancy was moderately associated with subnormal attention and executive function in the offspring at age 5." The study examined the impact of maternal use of paracetamol during pregnancy on the attention of children at age 5 years. The study involved 1491 mothers and children enrolled in the Danish National Birth Cohort. First-trimester use of paracetamol was associated with poorer attention scores in childhood, and children prenatally exposed to paracetamol were at a higher risk for subnormal overall attention, selective attention difficulties, and parent-rated subnormal executive function. The risks for subnormal overall attention or executive function were elevated with longer duration of paracetamol use in pregnancy. The odds ratios were OR = 1.5, 95% CI 1.0, 2.5 for subnormal overall attention, OR = 1.5, 95% CI 1.0, 2.4 for selective attention difficulties, and OR = 1.5, 95% CI 0.9, 2.3 for parent-rated subnormal executive function. A subset of mothers reported the trimester in which they used acetaminophen; trimester specific ORs where in overall stronger (up to OR=2.8 for sustained attention and acetaminophen use in the first trimester) than those for ever/never use during pregnancy; it is possible that these stronger associations reflect better recall and lower misclassification of the drug use.

Liew et al. (2014),[9] which was reviewed earlier in this document, "found that prenatal exposures to acetaminophen may increase the risk in children of receiving a hospital diagnosis of HKD or ADHD medication and of exhibiting ADHD-like behavior." The study investigated 64,322 mother-child pairs in Denmark enrolled in the Danish National Birth Cohort during 1996-2002. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of hyperkinetic disorder (HR = 1.37; 95% CI, 1.19-1.59), use of ADHD medications (HR = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (RR = 1.13; 95% CI, 1.01-1.27). The authors presented a stratified analysis showing HRs for autistic spectrum disorders with hyperkinetic symptoms, which showed no meaningful difference in the HR linking prenatal acetaminophen and the outcome across group of women who reported different type of indications for using the medication (See table below).

Supplemental Table 3. Hazard Ratios (HR) for autistic spectrum disorders with hyperkinetic symptoms in children and prenatal acetaminophen use, excluding mothers with specific health conditions during pregnancy

Acetaminophen use during pregnancy	Autism spectrum disorders			
	Hyperkinetic -		Hyperkinetic +	
	No. Cases	Adjusted HR[a] (95% CI)	No. Cases	Adjusted HR[a] (95% CI)
Among mothers who did not have fever, inflammation and infections during pregnancy				
Never used	205	1.00 (ref)	75	1.00 (ref)
Ever used	232	1.07 (0.88-1.31)	137	1.72 (1.26-2.34)
All three trimesters	50	1.23 (0.90-1.69)	27	1.85 (1.17-2.93)
>20 weeks	28	1.48 (0.98-2.23)	12	1.83 (0.98-3.42)
Among mothers who did not have diseases in muscles/joints during pregnancy				
Never used	266	1.00 (ref)	97	1.00 (ref)
Ever used	350	1.06 (0.89-1.27)	273	1.50 (1.14-1.98)
All three trimesters	70	1.25 (0.96-1.65)	35	1.67 (1.11-2.50)
>20 weeks	34	1.41 (0.98-2.02)	14	1.57 (0.89-2.78)
Among mothers who did not suffer in psychiatric illness during pregnancy				

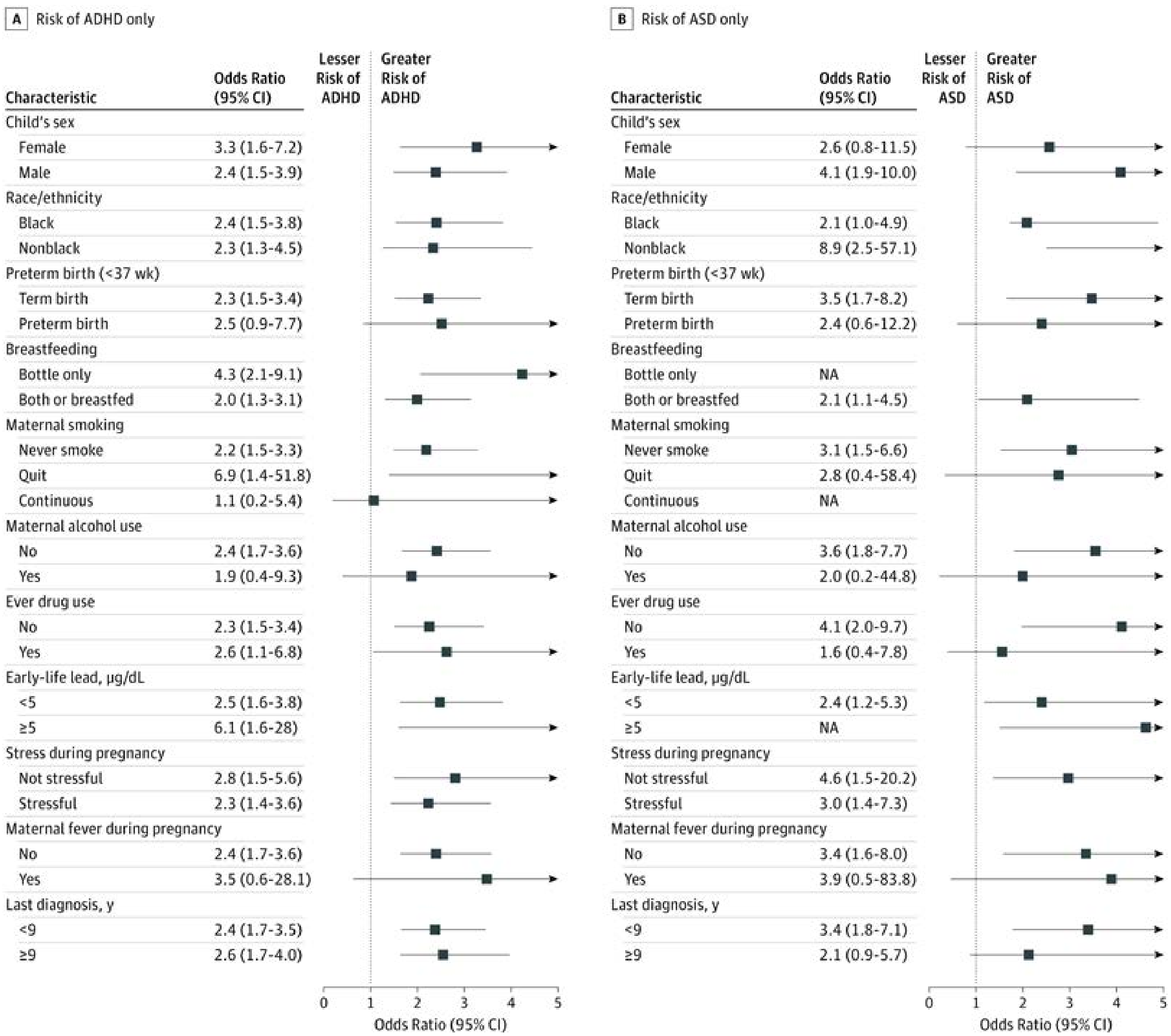
Never used	268	1.00 (ref)	90	1.00 (ref)
Ever used	344	1.05 (0.88-1.26)	180	1.65 (1.25-2.18)
All three trimesters	69	1.19 (0.90-1.57)	38	1.87 (1.25-2.79)
>20 weeks	33	1.28 (0.88-1.87)	17	1.92 (1.13-3.25)

[a] Adjusted child's sex, birth year, maternal age at birth, parity, socio-economic status, maternal smoking and alcohol drinking during pregnancy, maternal pre-pregnancy body mass index, folic acid intake during pregnancy, maternal use of ibuprofen and aspirin during pregnancy. Mother's psychiatric illnesses, maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy were included in the model except when we exclude mothers with that specific health condition in analysis.

Avella-Garcia 2016,[190] also one of the papers I described earlier in this report, is a Spanish birth cohort study with 2644 mother-child pairs; prenatal exposure to acetaminophen was assessed for its association with neurodevelopmental outcomes at 1 and 5 years of age. The results showed that offspring ever-exposed to acetaminophen had a higher risk of presenting more hyperactivity/impulsivity symptoms, increased commission errors in the Conner's Kiddie Continuous Performance Test (K-CPT), and lower detectability scores. In males, the Childhood Autism Spectrum Test (CAST) scores were increased among those ever-exposed. The effect sizes of these risks were further increased with higher frequency of acetaminophen use. Additional analyses were performed excluding mothers reporting: (i) fever; (ii) chronic illness; (iii) urinary tract infection; or (iv) any of these three conditions, during pregnancy; as well as analyses including only mothers whose indication for acetaminophen use was pain control or infection. The results of these analyses were similar to those in the main analysis that included all participants together, following the same direction of the effect and dose-response trends for acetaminophen.

Ji et al. (2020),[165] examined the association between cord plasma acetaminophen metabolites and the risk of attention-deficit/hyperactivity disorder, autism spectrum disorder (ASD), and other developmental disabilities (DDs) in childhood. The analysis included 996 mother-infant dyads from the Boston Birth Cohort, with follow-up at the Boston Medical Center. Three cord acetaminophen metabolites were measured, and physician-diagnosed ADHD, ASD, and other DDs were assessed through medical records. The study found that compared to the first tertile, being in the second and

third tertiles of cord acetaminophen burden was associated with higher odds of ADHD diagnosis (OR for second tertile: 2.26; 95% CI: 1.40-3.69; OR for third tertile: 2.86; 95% CI: 1.77-4.67) and ASD diagnosis (OR for second tertile: 2.14; 95% CI: 0.93-5.13; OR for third tertile: 3.62; 95% CI: 1.62-8.60). As shown in the figure below, the authors also estimated the effect of acetaminophen on ADHD/ASD among subgroups, including subgroups by indication for taking acetaminophen. The point estimates of the associations between cord acetaminophen burden and ADHD and cord acetaminophen burden and ASD were in the positive direction across strata of these variables. Specifically, the authors reported that "sensitivity analyses and subgroup analyses found consistent associations between acetaminophen and ADHD and acetaminophen and ASD across strata of potential confounders, including maternal indication, substance use, preterm birth, and child age and sex, for which point estimates for the ORs vary from 2.3 to 3.5 for ADHD and 1.6 to 4.1 for ASD."



As demonstrated by the description of each of the studies, the investigations I described here above consistently showed that prenatal acetaminophen use has a detrimental effect on the risk of developing ADHD and ASD in children, irrespective of whether the medication was used to treat fever or other indications. Specifically, the stratified analysis reported in these studies consistently showed similar effects of prenatal acetaminophen on child's ADHD/ASD for mother taking the medication because of fever and for mothers taking it for other reasons.

Gustavson, 2019,[170] analyzed data from the Norwegian Mother and Child Cohort Study, which included over 114,000 children. The study examined the relationship between maternal fever and ADHD in offspring. Children exposed to maternal fever during the first trimester had a higher likelihood of receiving an ADHD diagnosis compared to unexposed children OR = 1.31, 95% CI = 1.06-1.61. For children exposed to maternal fever twice or more during the first trimester, the odds ratio increased to 2.64 (CI = 1.36-5.14). Furthermore, using linear regression analysis, the authors observed elevated inattention symptoms among children exposed to fever in both the first (Cohen's d = 0.09, CI = 0.03-0.15) and second (Cohen's d = 0.05, CI = 0.01-0.09) trimesters. However, hyperactivity/impulsivity symptoms did not show a significant association with maternal fever. This risk was not influenced by the use of acetaminophen to alleviate maternal fever. Whether or not acetaminophen was used, the association between maternal fever and ADHD remained consistent.

Hornig et al. (2018),[181] used a prospective cohort in Norway to examine the association between fever and ASD. Maternal exposure to second-trimester fever was associated with increased ASD risk (adjusted odds ratio (aOR), 1.40; 95% confidence interval, 1.09-1.79), with a similar, but nonsignificant, point estimate in the first trimester. Risk increased markedly with exposure to three or more fever episodes after 12 weeks' gestation (aOR, 3.12; 1.28-7.63). In secondary stratified analyses, they examined whether use of acetaminophen for fever modified fever-associated ASD risk, as shown in the table below. Risk tended to be moderately lower within each trimester in febrile women who took acetaminophen for fever than in febrile women who did not. However, the confidence intervals for the estimates were large and overlapping, indicating that the difference between strata of acetaminophen use did not meet the criteria for statistical significance.

Supplementary Table S6A. Association between maternal fever and risk of ASD in offspring, with acetaminophen as effect modifier, by trimester (respondents to Q1, Q3 and Q4; N=79 109[1]).

Exposure period	Exposure stratum[2]	ASD exposed N (%)	Non-case exposed N (%)	Crude model				Adjusted models											
				OR	95% CI		*p*-value	aOR1[3]	95% CI		*p*-value	aOR2[4]	95% CI		*p*-value	aOR3[5]	95% CI		*p*-value
First trimester	Fever with acetaminophen	5 (1.05)	823 (1.05)	1.02	0.42	2.47	0.967	0.99	0.41	2.40	0.979	1.13	0.47	2.74	0.789	1.07	0.44	2.61	0.875
	Fever without acetaminophen	15 (3.16)	1 688 (2.15)	1.49	0.89	2.50	0.130	1.41	0.84	2.36	0.198	1.48	0.88	2.48	0.140	1.38	0.82	2.32	0.226
Second trimester	Fever with acetaminophen	40 (8.44)	5 599 (7.12)	1.23	0.89	1.71	0.206	1.24	0.89	1.72	0.203	1.37	0.99	1.90	0.060	1.37	0.98	1.90	0.064
	Fever without acetaminophen	36 (7.59)	4 270 (5.43)	**1.46**	**1.03**	**2.05**	**0.031**	1.41	1.00	1.99	0.052	**1.49**	**1.05**	**2.10**	**0.024**	**1.44**	**1.02**	**2.03**	**0.040**
Third trimester	Fever with acetaminophen	5 (1.05)	1 249 (1.59)	0.67	0.28	1.61	0.367	0.64	0.26	1.56	0.326	0.76	0.32	1.85	0.551	0.72	0.30	1.75	0.472
	Fever without acetaminophen	12 (2.53)	1 357 (1.73)	1.47	0.83	2.62	0.189	1.38	0.77	2.46	0.274	1.46	0.82	2.61	0.196	1.37	0.77	2.45	0.288

Key: aOR, adjusted odds ratio; **ASD**, autism spectrum disorder; **CI**, confidence interval; **OR**, odds ratio (**red bold** text represents significant values, *p*<0 05)

1 ASD, N=474; Non-case, N=78 635

2 Risk of ASD in each stratum of fever-exposed women (with or without use of acetaminophen for fever) is as compared to the reference group of women who did not have fever and, by extension, did not use acetaminophen for fever (this reference group of women may have used acetaminophen in the same trimester for other, non-fever indications)

3 aOR1: adjusted for presence of fever in the other trimesters (*Adjusted Model 1*)

4 aOR2: adjusted for maternal age, smoking, parity; parental education; birth year (*Adjusted Model 2*)

5 aOR3: adjusted for presence of fever in the other trimesters and confounder variables (maternal age, smoking, parity; parental education; birth year) (*Adjusted Model 3*)

Zerbo et. al. (2013)[179] was a small case control study designed to "assess associations with maternal influenza or fever during pregnancy," in particular ASD and developmental delays. The study found that ASD and developmental delays were not associated with influenza but were associated with maternal fever during pregnancy, though that risk was attenuated among mothers who reported taking antipyretic medications. Specifically, the study found that "children whose mothers reported fever but took anti-fever medications had comparable odds for ASD as those whose mothers did not have fever during pregnancy." The authors interpreted this study to suggest that use of antipyretic medications during pregnancy may be beneficial to the developing fetus with regard to autism spectrum disorders. This study had serious limitations. It utilized a case control design—generally considered inferior to the large cohort studies discussed here—the authors noted that the "results [could] potentially be affected by recall bias," and the study was relatively small. The study did not examine the effect of acetaminophen specifically, instead grouping acetaminophen together with a number of other antipyretic medications—including ibuprofen, Excedrin, and many others—severely limiting the ability of this study to provide reliable evidence on the association between acetaminophen and ASD. Finally, the study focused only on women who had fever and influenza in pregnancy, and not on women who took antipyretic medications for indications other than fever, *e.g.*, minor pain relief.

In summary, studies examining whether the possible adverse effect of maternal fever during pregnancy on ADHD/ASD are somewhat ameliorated by acetaminophen use have yielded mixed results. However, two of the three studies reviewed above suggest that taking acetaminophen to alleviate fever during pregnancy may help reduce the adverse effects of the fever. Mothers who experience fever and take acetaminophen are exposed to three different forces: 1. the possible negative impact of the fever on the developing brain; 2. the positive effects of acetaminophen in reducing the fever; and 3. the possible negative effects of acetaminophen on the developing brain.

While acetaminophen may have some beneficial effects in mitigating the impact of fever, particularly in cases of high or prolonged fever, it is important to consider that the overall impact on the developing brain may be influenced by multiple factors. These factors include the level and duration of the fever, the dose and duration of acetaminophen use, and the extent to which fever reduction is achieved through acetaminophen administration.

In conclusion, the interplay between prenatal fever, acetaminophen use, and their effects on the developing brain is complex. The studies investigating whether the adverse effects of prenatal

acetaminophen on ADHD/ASD is modified by the type of indication consistently showed no difference between use due to fever vs. other indications. The data currently available on whether acetaminophen use reduces the effects of prenatal fever are limited and provide incomplete information to understand the nuanced interactions among fever and acetaminophen and their implications for neurodevelopmental outcomes in children. Importantly, fever has not been associated with either ADHD or ASD in the third trimester.

5. Literature Reviews

Olsen and Liew (2017),[10] reviewed the existing evidence to argue in favor of warning pregnant women about the neurodevelopmental risks of maternal acetaminophen use. The authors noted that existing evidence "from several cohorts and different analytical options" have "increased the probability that the association is causal." The authors noted that "the studies we are aware of covering the topic of fetal programming all find statistically significant results."

The authors also emphasized that "it is too simple and not justified to explain away the possibility of causality by mentioning confounding, especially confounding by indication," because such speculation about confounding "has to be supported by stronger evidence, not just opinions." They doubted confounding as an explanation for the observed association because the "triangulation approach"—whereby "a bias problem" is "approached from different angles" – suggested that confounding could not explain the results. Indeed, the authors noted that these analyses "have consistently suggested that confounding alone is an unlikely explanation for this disturbing observation." As the authors noted numerous studies have "tr[ied] to make the association 'go away'" but were not successful in doing so. The authors ultimately concluded that "the time has come for some precautionary action" and that "mothers-to-be should at least be advised to avoid the drug if treatment is not necessary for her conditions" since "taking the drug frequently might have health consequences for the unborn child."

Bauer and Kriebel (2018),[7] performed a systematic review of nine prospective cohort studies. All nine of the studies "suggested an association between APAP exposure and the neurodevelopmental outcomes: ADHD, ASD, or lower IQ." The study authors noted that these studies "provide a strong body of evidence suggesting neurodevelopmental effects of prenatal APAP exposure," and that "several lines of reasoning suggest that bias, confounding and chance are not solely responsible for the observed relationships." The authors noted that the studies showed consistency and dose response and that the causal association was biologically plausible. And they noted that their findings "argue against a

spurious association," *i.e.*, argue against confounding alone being able to explain the association between prenatal acetaminophen exposure and NDDs. Although the authors noted that "residual confounding" was still a concern, and that limitations in the study limited the ability to make a causal inference, the authors ultimately concluded that "these nine studies suggest an increased risk of adverse neurodevelopmental outcomes following prenatal APAP exposure" and that "pregnant women should be cautioned against indiscriminate use of APAP" given the "substantial public health implications."

Bauer, et. al is a consensus statement published by 91 scientists, clinicians and public health professionals from across the globe.[2] The authors were motivated by the "disturbing increases in the number of children with cognitive, learning and/or behavioural problems." As the consensus-statement authors noted, the "relationships between prenatal APAP exposure and adverse neurodevelopmental outcomes have been investigated in 29 observational studies in 14 cohorts including over 220,000 mother–child pairs from different parts of the world" with a full 26 of those studies identifying "positive associations with APAP exposure during pregnancy and a range of clinically assessed and parent-reported neurodevelopmental outcomes, primarily attention deficit hyperactivity disorder (ADHD)." Although the authors noted that there were remaining theoretical concerns about "potential confounding," "several analytical techniques have been used to control for confounding by indication, with results largely remaining unchanged" and "similar disease risk observed across different indications supports a causal association." The authors also noted that the large effect sizes seen in many of the studies make "residual confounding by uncontrolled factors is a less likely explanation for identified associations." Although the authors did not make a definitive conclusion that the association was causal, they noted that society need not "wait for unequivocal proof that a chemical is causing harm to our children" before taking action. And they believed that "the combined weight of animal and human scientific evidence is strong enough for pregnant women to be cautioned by health professionals against [acetaminophen's] indiscriminate use." The authors ultimately recommended that "pregnant women should be cautioned at the beginning of pregnancy to: forego APAP unless its use is medically indicated; consult with a physician or pharmacist if they are uncertain whether use is indicated and before using on a long- term basis; and minimize exposure by using the lowest effective dose for the shortest possible time." As they noted, "[g]iven the high prevalence of APAP use by pregnant women, the public health implications of use reduction might be substantial."

The publication of the consensus statement has led to additional debate among epidemiologists. In Damkier et al. (2022),[195] the authors questioned the conclusions of the consensus statement, although

they admitted that the consensus statement authors "reflect appropriately upon the inconsistencies and limitations of the underlying data" and supported "their call for better data." They also agreed that "APAP should be used by pregnant women cautiously at the lowest effective dose for the shortest possible time." And they conceded that "preclinical data might support some mechanistic aspects of" a causal interpretation of the observed association. But they questioned drawing "clinical conclusions" from the data, the use of parent and teacher "questionnaires" to determine outcomes, and a purported failure to account for "hereditary aspects of" ADHD and ASD, which they viewed as a potential confounder. Damkier and another author raised similar concerns in Damkier and Hodson (2022),[196] as did O'Sullivan et al. (2022).[197]

In Alwan et al. (2022)[198], a group of 50 scientists, clinicians, and teratology information specialists affiliated with the "Organization of Teratology Information Specialists", published what they deemed a "consensus counterstatement to the conclusion" of the Bauer Consensus Statement.[198] The counterstatement, with no factual support, makes global assertions with respect to all acetaminophen studies that they are "limited by serious methodological problems, including to account for confounding and elements of bias that make interpretation of the data challenging" [198] Additionally, they claim (again without stating any basis for the claim) that "differential exposure and misclassification of the timing, dose and duration of use of APAP during pregnancy is likely."[198] They provide no explanation why they believe differential misclassification (which would overstate the risk) is likely, nor do they address the comments of the study authors and reviewers that misclassification, if any, would be non-differential misclassification which would result in an under-estimation of the risk.

Alwan et al. (2022), also attempt to cast doubt on the conclusions of the Bauer consensus statement by asserting that "the quality and validity of neurodevelopmental outcome definitions are 'problematic'".[198] In support of this vague assertion, they cite to a Letter to the Editor published by Damkier et al. (2015)[199], criticizing the use of such definitions in the study by Brandlistuen et al. (2013),[14] (discussed above at G.3.). Brandlistuen et al. (2015), thoroughly dispatched with Damkier's criticisms (and also of the suggestion that confounding by indication could explain the association seen) by demonstrating that Damkier's critiques were "erroneous and is not a correct summary of the published findings."[200]

It is unclear if Alwan et al. were unaware of the detailed reply to Damkier et al.'s letter to the editor by Brandlistuen et al. or if they consciously chose to ignore it. Alwan et al. also failed to acknowledge or address the analyses that have been done to address and dispatch with their claims of "serious

methodological problems" concerning confounding and misclassification. (See discussion of confounding and misclassification above.)

In short, the consensus counterstatement by Alwan et al., raises theoretical criticisms globally of acetaminophen studies without undertaking any analysis of those issues or acknowledging the work by numerous researchers who have previously addressed them.

In my view, the authors of these responses underestimate the real and enduring strength of the literature. As detailed above, the association between prenatal acetaminophen use and neurodevelopment disorders has persisted despite numerous attempts to link it with any sort of confounding. These efforts include numerous studies that controlled directly for a wide range of potential confounders as well as studies that used innovative techniques to assess whether unmeasured or residual confounding might explain the observed association between prenatal acetaminophen exposure and NDDs. The weight of those studies does not suggest that confounding can explain the association, leaving causation as by far the most likely explanation for the association. At best, the authors of these responses raise theoretical sources of confounding that, although impossible to definitively disprove, are essentially based on speculation and conjecture alone. The actual evidence does not suggest that confounding can fully explain the observed associations, as numerous authors have pointed out.

The authors of the consensus statement responded to the criticisms in two replies published in Nature. In Bauer et al. (2022;18(3):192-192)[201], the consensus statement authors responded to the Damkier and Alwan criticisms described above. They reiterated their belief that "available data provide sufficient evidence for concern and a recommendation of precautionary action." As they pointed out, the "observational data" from the epidemiology is entirely "consistent" with "a large body of experimental data" including "animal studies, which are not subject to confounding or bias," providing "an essential source of evidence and support for causality." Although they noted that they had not included an "inference of causality" in their consensus statement, and joined the call for additional research, the authors reiterated that there was a "consistent signal" that required action. They ultimately adhered to their previous conclusion: "women should be cautioned from early pregnancy to use APAP only when indicated, at the lowest dose and for as short a time as possible."

In Bauer et al, (2022;18(6):386-386)[202], the consensus statement authors responded to the criticisms noted in the O'Sullivan response described above. Although they agreed with the request for "more

well-designed studies of APAP use in pregnancy," they nevertheless reiterated that the existing literature was based on a "large amount" of data showing a "high degree of consistency between the human and experimental studies." As a result, they repeated their recommendation that "until proven safe for use in pregnancy by further studies, APAP use in pregnancy should be minimized." They noted that an "APAP-specific risk communication is warranted for pregnant women due to the widespread accessibility of this over-the-counter medication and the common perception of negligible risk." In their view, "pregnant women and their health professionals deserve to be informed of the potential risks in order to make the best possible decisions regarding use."

I agree with that assessment. Causation is far and away the most likely explanation for the observed association between prenatal acetaminophen exposure and NDDs such as ADHD and ASD, which means women need to be fully informed of the relevant risks to allow them to make informed decisions about whether to use acetaminophen while pregnant.

Patel et al. (2022),[25] investigated "the available evidence on the long-term safety of prenatal and neonatal paracetamol [acetaminophen] exposure." Specifically, the authors "conducted a systematic search of the electronic databases Ovid Medline, Ovid Embase and Web of Science from inception to August 2021 for original research studies of any design that described the use of paracetamol in the prenatal or neonatal (within the first four weeks of life) periods and examined the occurrence of neurodevelopmental, atopic or reproductive adverse outcomes at or beyond birth." 100% of the eleven studies they reviewed on the relationship between prenatal acetaminophen use and neurodevelopmental outcomes "reported adverse neurodevelopmental" outcomes. As the authors note, "impaired neurodevelopment was reported in 11 studies, with specific reports of increased conduct problems," "ADHD," "hyperactivity symptoms," "motor milestone delays," and "hyperkinetic disorders" "among children with prenatal paracetamol exposure." The authors also assessed the risk of bias in the studies using the Newcastle-Ottawa Quality Assessment Scale. All but three of the cohort studies examined received "a rating between seven and nine, indicating a low risk of bias." The authors ultimately concluded that "the results of the current systematic review suggest that prenatal exposure to paracetamol [acetaminophen] is associated with an increased risk of neurodevelopmental" adverse outcomes. They recommended that "the safety advisory committees of drug-regulatory agencies" needed to investigate "the currently existing information" "so that timely appropriate labeling updates can be made and accessed by consumers and healthcare providers."

Khan et al. (2022),[22] conducted a study "to review the published papers investigating maternal acetaminophen (AP) use during pregnancy and its effect on the offspring's neurodevelopment, particularly autism spectrum disorders." After screening dozens of studies using quality assessment tools for each study design, they made a final selection of "16 high quality papers" including 12 prospective cohort studies, two review articles, and one meta-analysis. In their view "all the studies were showing similar results," namely that "acetaminophen use during pregnancy is associated with several NDDs, including ASD and ADHD." Based on their review, they found that "[l]ong-term acetaminophen use was more strongly associated with the outcomes in a dose-response fashion." And on the issue of confounding, they stated that they "did not see the confounding effects of other risk factors for NDDs." The authors ultimately concluded that, based on "sufficient data from multiple populations," "acetaminophen is not as safe as it is considered." Their recommendation was that pregnant women "should have limited use of this analgesic until proven otherwise."

In the Twelfth Edition of *Briggs Drugs in Pregnancy and Lactation* 2022[19], a "reference guide to fetal and neonatal risk" that is widely considered an authoritative textbook in the field, the editors conducted a review of the literature concerning prenatal acetaminophen exposure and NDDs. The review included a number of the papers discussed above, such as Brandlistuen, Stergiakouli, Ystrom, Avella-Garcia, and several of the Liew papers. The textbook provides "pregnancy recommendations" designed "to assist the reader in determining the level of risk of a specific drug." For acetaminophen, the Briggs textbook's pregnancy recommendation states that "long-term use suggests risk." The textbook goes on to state that "although originally thought not to *cause* harm, this assessment much *change* because of recent data" linking several weeks' worth of prenatal acetaminophen use to "decreased IQ, ADHD, and other problems in neurodevelopment." The textbook concludes that, although "the drug should not be withheld if required for maternal fever," "routine use of acetaminophen should be avoided" by pregnant women.

H. CAUSAL ASSESSMENT AS TO WHETHER PRENATAL USE OF ACETAMINOPHEN CAN CAUSE NDDS INCLUDING ADHD AND ASD.

1. Summarizing the Evidence Using the Navigation Guide Methodology

As recommended by the Navigation Guide approach, I provided a final determination about the toxicity of prenatal acetaminophen use. As recommended by Woodruff and Sutton[27] for the Navigation Guide, the final determination combines the evidence from observational human studies as well as from experiments in vitro and organism models. For each question, the end result is one of the following five

possible statements about the overall strength of the evidence: “known to be toxic,” “probably toxic,” “possibly toxic,” “not classifiable,” or “probably not toxic.”

a. Is Acetaminophen Use During Pregnancy Causally Associated with ADHD?

i. Grading Risk of Bias of Each Study on Prenatal Acetaminophen and ADHD

I rated each of the ADHD studies for risk of bias utilizing the approach outlined above. The results of my ranking are detailed in Appendix 1.

1) Selection

All studies I reviewed were prospective cohort studies where pregnant women were enrolled during pregnancy or at delivery and their children assessed for ADHD years later. Therefore, in these studies all participants were enrolled—during pregnancy or shortly after delivery—regardless of their exposure to prenatal acetaminophen. Mother and child pairs were then followed up over time for many years and children were assessed to evaluate ADHD symptoms and/or diagnosis. Therefore, there was no knowledge at enrollment of their ADHD status. Because of their prospective nature, the studies were not typically susceptible to these sources of bias and therefore I rated nearly all studies at “low risk of bias.” The only exception was the study by Chen et al. (2019).[171] This article reports results from a prospective study based on the nationwide Taiwan cohort. While the study design is similar to the others and the methods for inclusion into the nationwide cohort were sound, this publication used a nested-case control design in which cases of ADHD and non-ADHD controls were matched based on mothers’ ages, children’s sex and ages, mothers’ age during pregnancy, income, and urbanization level. In case-control studies, matching variables also need to be included in the regression model evaluating the association of interest to avoid a situation known as “overmatching,” which can make the exposure of interest artifactually similar between cases and controls.[203] In other words, without including the matching variables as covariates in the final analysis, the study would fall under the designation “protocols for recruitment or inclusion/exclusion criteria applied differently across study groups” described above, because all cases were included while the authors included only controls with certain characteristics that made them more similar to the cases than they were in the entire study population. This is done typically to increase statistical efficiency and reduce costs or computation burden, but it is well known to introduce bias if proper corrections to rebalance the study groups are not applied in the final statistical analysis.[203] Chen et al. (2019),[171] do not clarify whether all the matching variables were included or not in the regression models. If they were not included, that would cause underestimation

of the association between prenatal acetaminophen and ADHD.[203] Therefore, I rated this paper as "probably high risk of bias" (score = 3) because there was insufficient information about the matching variables to permit a judgment of "high risk of bias", but there was concern that the matching scheme used for including controls in the study was not properly adjusted for in the analysis.

2) Blinding

All the studies evaluated were prospective and therefore not subject to blinding issues or recall bias. Therefore, I rated all studies at low risk of bias (score = 1). In summary, there is no concern about blinding in the literature I examined.

3) Exposure Assessment

Two studies directly measured acetaminophen in cord blood (which is fetal blood) or in meconium. Because of the direct, objective measurements of acetaminophen, I rated these two studies at low risk of bias (score = 1). The other studies assessed acetaminophen use during pregnancy through questionnaires administered to the mothers either during pregnancy or shortly after delivery. I rated these studies at "probably low risk of bias" (score = 2). However, my review identified one study using maternal self-reports that appeared to have lower quality data. Tovo-Rodriguez, 2018[169] reported low rates of acetaminophen use during pregnancy (27.5%); these rates were much lower than those recorded previously in the same study population (51%). Therefore, it is highly likely that acetaminophen use was grossly underreported. Therefore, I rated this study at "high risk of bias" (score = 4). Overall, the average score across the 13 studies for exposure assessment was 2, which indicates probably low risk of bias overall. It is worth noting that because of the prospective nature of the studies, the misclassification of the exposure is expected to be unrelated to the outcome (i.e., non-differential). This type of misclassification is expected to dilute the signal, because some exposed mother-child pairs are classified as unexposed, and vice versa some unexposed mother-child pairs are classified as exposed. Therefore, I believe that the real magnitude of association to be higher than that reported by most studies. Indeed, the two studies that used objective measurements of acetaminophen in cord blood or meconium showed higher relative risks of ADHD (OR=2.43 in Baker et al. (2022); ORs of 2.26 [2nd tertile] or 2.86 [3rd tertile] in Ji et al. (2020). It is therefore likely that the use of maternal self-report attenuated the magnitude of relative risks estimated by the studies and that the actual effects are substantially stronger.

4) Outcomes

Based on the above criteria, I rated six studies as “low risk of bias”, eight studies at “probably low risk of bias”, and one study at “probably high risk of bias”.

5) Confounding

My review showed that most studies accurately evaluated potential confounders and used appropriate methods for adjusting for confounding variables. I rated ten studies as “low risk of bias,” four studies as “probably low risk of bias,” and one study as “high risk of bias.” My decision to rank one study as a four was based upon the sibling control design, while intended by the authors to control for unmeasured confounding, also eliminated the effect mediated by intermediate variables and likely biasing the results toward the null. My decision to rate studies that did not control for confounding by indication at “probably low risk of bias” (score = 2) was also supported by my review of the literature: the studies that evaluated confounding by indication in the context of prenatal acetaminophen and ADHD showed minimal differences after adjusting for confounding by indication relative to the estimates that did not adjust for this type of confounding. Therefore, these studies do not support the concept that confounding by indication is a relevant source of bias for the associations between prenatal acetaminophen and ADHD.

6) Incomplete Data

Based on my review, I rated 10 studies as having a "low risk of bias" with respect to incomplete data, meaning that they adequately addressed missing data and produced reliable results. Five studies were rated as "probably low risk of bias," indicating that they likely addressed missing data appropriately, but with some limitations.

7) Selective Reporting

Upon reviewing the studies, I found no evidence of selective outcome reporting across the studies. However, it is important to note that my evaluation was based solely on the information that was reported in each of the papers. It is possible that selective reporting may have occurred but was not apparent from the information that was presented.

8) Conflict of Interest

Based on my review of the studies, 13 studies were rated as 1 (“low risk of bias,”) and 2 studies were rated as 3s (“probably high risk of bias”) due to a conflict between the editorial board and a study author.

9) Other Sources of Bias

In my review, I did not find that any study suffered from other problems that were not addressed above.

ii. Summary of Risk of Bias in ADHD Studies

Upon reviewing the studies, I found that the average of my scores across all nine possible sources of bias was equal to 1.2, indicating that, on average, studies were appropriately conducted, and bias was well prevented and/or controlled in the studies. However, it is important to note that not all sources of bias carry equal weight. In some cases, a single source of bias can heavily influence the study results and conclusions. For this reason, the Navigation Guide recommends that experts review the quality of the studies. In order to account for potential limitations and weaknesses in the studies, I used my findings to downgrade the strength of evidence provided by studies that were deemed to be lower quality due to individual sources of bias that might weighted heavily on the results. This process was part of the "grading of the strength of evidence", as described in the next section.

By carefully evaluating potential sources of bias and downgrading studies based on their quality, I was able to provide a comprehensive assessment of the available evidence on the causal relationship between acetaminophen during pregnancy and risk of ADHD. This approach allowed me to make more informed judgments about the reliability and validity of the studies, and to provide a rigorous analysis of the current state of evidence on this topic.

iii. Grading Strength of Evidence of Each Study on Prenatal Acetaminophen and ADHD

I rated each of the ADHD studies for strength of evidence utilizing the approach outlined above. The results of my ranking are detailed in Appendix 1.

1) Sample Size

I scored five studies, four studies with sample size >5,000 and 1 case-control study with 950 cases of ADHD and 3800 controls, at +2, five studies with sample size between 1000-5000 at +1, two studies with sample size between 500-999 at 0, and three with sample size between 250-499 at -1. No study had sample size <250, which would have called for a -2 score. The scoring distribution reflects the large sample size of most studies. For case-control studies, because ADHD has a cumulative incidence rate of approximately 10% in children (i.e., one out of 10 children will be diagnosed with ADHD), I had predetermined to multiply the number of cases by 10 to compare the sample size to that of the cohort

studies. The largest study, Ystrom et al. (2017),[11] included 112,973 participants. The smallest study, Streissguth et al. (1987),[166] included 355 participants.

2) Large Effect

I scored four studies at +2 (relative risk >2), two studies at +1 (relative risk between 1.5-2.0), seven studies at 0 (relative risk between 1.0-1.5 and statistically significant results), and two studies at -1 (non-statistically significant associations). No study qualified for the -2 score (significant association indicating that prenatal acetaminophen protects children against ADHD). Most studies showed moderate effect size (score=0). However, the two studies that showed large effects (score = +2) were the two studies that used objective measurements of acetaminophen in cord blood or meconium to confirm the exposure. This finding suggests that the other studies may be subject to measurement error in the classification of the exposure; this type of measurement error, because of the prospective design of all studies, is expected to be independent of ADHD outcomes and therefore bias the results toward the null. It is worth noting that most studies showed a statistically significant association linking prenatal acetaminophen with ADHD and no study showed a protective association.

3) Exposure-response Relationship

I scored five studies at +2 (evidence of an exposure-response relationship) and ten studies at 0 (no evidence of an exposure-response relationship). Most of the studies that provided no evidence of an exposure response association did not report an exposure response analysis, in some cases due to limited sample size that made such analysis not feasible.

4) Internal Consistency

I scored eight studies at +2 (findings with high degree of consistency), five studies at +1 (moderate/medium consistency), one study at 0 (moderate consistency), and one study at -1 (some inconsistency or lack of clarity.) The majority of the studies showed a high level of consistency.

5) Control of Bias

The studies used a variety of precautions and study designs that limited bias (e.g., prospective design, statistical analyses addressing confounding and loss to follow up, etc.). This is expected in well-designed studies. If the study was well-designed and executed with very low risk potential sources of bias, I left the score at 0. Indeed, the studies used state of the art epidemiology techniques to address and correct bias. However, some types of bias, e.g. that due to measurement errors of the exposure and/or

outcomes, are still possible. Therefore, I scored only three studies at +2 (very low risk of bias). I scored six studies at +1 (low risk of bias); these studies provided solid control of bias and typically controlled by adjustment by indication. I scored three studies at 0 (moderate risk of bias), one study at -1 (high risk of bias), and two studies at -2 (very high risk of bias). Specifically, the study scored at -1 did not provide enough information to confirm that potential bias from the matching between cases and controls was controlled for in regression analysis; failure to control for the matching design would bias the results toward the null. It is worth noting that except for confounding by indication, all the sources of bias I examined (e.g., overmatching, measurement error/misclassification of exposures or outcomes) would bias the results toward the null.

6) Other Factors

For the overwhelming majority of all studies, I identified no other factors that could not be classified in one of the categories above. However, I used the category "other factors" to note the strengths of two studies (+2) (Baker et al. (2022),[204] and Ji et al. (2020),[165] and the weakness of two studies (-1), Gustavson et al. (2019)[170] and Gustavson et al. (2021).[173]

iv. Expert Opinion Score on the Overall Quality of Each Study on Prenatal Use of Acetaminophen and ADHD

I evaluated each of the ADHD studies to determine an expert opinion score following the approach outlined above. The results of my ranking are detailed in Appendix 1.

Based on my review of all the studies investigating the link between prenatal acetaminophen use and ADHD, I weighed some factors differently to create a final expert opinion score for each study. My analysis resulted in two upgrades of the initial scores. I upgraded one study from +1 to +2. This was because the study used extremely solid analytical methods, including negative control exposures and thorough consideration of confounding by indication, which reduced the chances of false positive findings. I downgraded one study from 0 to -1 due to concerns about small size and the bias toward the null likely introduced by the elimination of the effects of intermediate factors.

In conclusion, my expert opinion scores rated four studies at +2 (very strong evidence), five studies at +1 (strong evidence), four studies at 0 (moderate evidence), and two studies at -1 (weak evidence).

v. Final Determination Based on the Navigation Guide Analysis About the Toxicity of Prenatal Acetaminophen Use and Child's ADHD

Using the Navigation Guide approach described above, my final determination is that there is strong evidence of a causal link between prenatal acetaminophen use and an increased risk of ADHD in children. This determination is based on the evaluation of fifteen studies, including four high-quality studies that provided very strong evidence of an association and five studies that provide strong evidence of an association. The studies consistently reported a positive association between prenatal acetaminophen use and ADHD, with an exposure-response (dose-response) relationship observed in several studies. The evidence is supported by the robust study designs and methods, large sample sizes, and control for potential sources of bias and confounding. Furthermore, the consistency and coherence of the findings across multiple studies strengthens the evidence of the association. My determination is also supported by strong evidence about plausible mechanisms linking prenatal acetaminophen exposure and child's ADHD from experimental models.

Question addressed by the Navigation Guide analysis: can prenatal use of acetaminophen cause ADHD?

Final determination: Yes

Statement describing acetaminophen use during pregnancy in relation to child's ADHD: Based on current evidence and my Navigation Guide Analysis, I classify acetaminophen use during pregnancy as "Known to be Toxic" because of its ability to cause ADHD in children.

b. Is Acetaminophen Use During Pregnancy Causally Associated with ASD?

i. Grading Risk of Bias of Each Study on Prenatal Acetaminophen and ASD

I rated each of the ASD studies for risk of bias utilizing the approach outlined above. The results of my ranking are detailed in Appendix 1.

1) Selection

I reviewed six studies, five prospective cohort studies, where pregnant women were enrolled during pregnancy or at delivery and their children assessed for ASD years later, and one case-control study, where cases had been already diagnosed and controls recruited elsewhere (Saunders, 2019[155]). In the prospective cohort studies, all participants were enrolled—during pregnancy or shortly after delivery—regardless of their exposure to prenatal acetaminophen. Mother and child pairs were then followed up over time for many years and children were assessed to evaluate ASD. Therefore, in these cohort studies there was no knowledge at enrollment of the future ASD status of the children. Because of their prospective nature, the studies were not typically susceptible to differential (i.e., between children with and without ASD) bias and therefore, I rated these studies at "low risk of bias". In the case-control study, cases were determined using medical records, but controls were obtained from recruitment posters, hence the source of controls likely different from that of the cases; therefore, I rated the risk of selection bias for this study as "high risk of bias".

2) Blinding

As indicated above, recall bias may occur when information about prenatal acetaminophen use is collected after the informant (typically the mother) is aware that the child developed ASD. However, all the cohort studies evaluated were prospective and, therefore, not subject to recall bias. Therefore, I rated these studies at low risk of bias (score = 1). However, I rated the only case-control study available for my review as "high risk of bias."

3) Exposure

One study, Ji et al. (2020),[165]measured acetaminophen in cord blood (which is fetal blood). Because of the direct, objective measurements of acetaminophen, I rated this study at low risk of bias (score = 1). Most other studies assessed acetaminophen use during pregnancy through questionnaires administered to the mothers either during pregnancy or shortly after delivery. I rated these studies at "probably low risk of bias" (score = 2). However, my review identified one study using maternal self-reports that appeared to have lower quality data. Saunders et al. (2019),[155] used maternal self-reports of exposure at the time of the study (after ASD diagnoses), when children were between 0-10 years of age, implying a high chance of recall bias, particularly again in the setting of a case-control study. Therefore, it is highly likely that acetaminophen use was grossly underreported. Therefore, I also rated this study at "high risk of bias" (score = 4). Overall, the average score across the 6 studies for exposure assessment was 2.17, which indicates a probably low risk of bias overall. It is worth noting that because of the prospective nature of most studies, the misclassification of the exposure is expected to be unrelated to the outcome (i.e., non-differential). This type of misclassification is expected to dilute the signal, because some exposed mother-child pairs are classified as unexposed, and vice versa some unexposed mother-child pairs are classified as exposed. Therefore, I believe that the real magnitude of association to be higher than that reported by most studies. Indeed, the only study that used objective measurements of acetaminophen in cord blood or meconium showed a stronger association with ASD. It is, therefore, likely that the use of maternal self-report attenuated the magnitude of relative risks estimated by the studies and that the actual effects are substantially stronger.

4) Outcomes

Based on these criteria, I rated five studies as "low risk of bias", one study, Saunders et al. (2019),[155] at "probably low risk of bias", and none at "probably high risk of bias." The Saunders study used three different ways to determine ASD (patient charts, databases of four local pediatricians, and self-identification after seeing recruitment posters), creating concerns about heterogeneity in the diagnosis.

5) Confounding

My review showed that most studies accurately evaluated potential confounders and used appropriate methods for adjusting for confounding variables. I rated three studies as "low risk of bias", one study as "probably low risk of bias", and two, Leppert et al. (2019),[172] and Saunders et al. (2019),[155] studies as "high risk of bias". My decision to rate studies that did not control for confounding by indication at "probably low risk of bias" (score=2) was also supported by my review of the literature: the studies that

evaluated confounding by indication in the context of prenatal acetaminophen and ASD showed minimal differences after adjusting for confounding by indication relative to the estimates that did not adjust for this type of confounding. Therefore, these studies do not support the concept that confounding by indication is a relevant source of bias for the associations between prenatal acetaminophen and ASD.

6) Incomplete Data

The studies that I reviewed employed various methods to address incomplete data, such as imputation and multiple imputation of missing data. These methods allowed the researchers to make informed estimates of missing values, which can help to reduce bias in the study's findings. Furthermore, most of the studies reported that missing data were of low frequency, which suggests that the overall impact on the study's conclusions was likely minimal. Based on my review, I rated the six studies as having a "low risk of bias" with respect to incomplete data, meaning that they adequately addressed missing data and produced reliable results. Overall, by using appropriate methods such as imputation and multiple imputation, and reporting low frequency of missing data, these studies demonstrated a strong commitment to rigorous research methodology and high-quality data analysis.

7) Selective Reporting

Upon reviewing the studies, I found no evidence of selective outcome reporting across the studies. However, it is important to note that my evaluation was based solely on the information that was reported in each of the papers. It is possible that selective reporting may have occurred but was not apparent from the information that was presented.

8) Conflict of Interest

Based on my review of the studies, there was no evidence that the authors received support from a company, organization, or other entity having a financial interest related to the study questions. I specifically reviewed the funding or sponsorship of each study. However, it's important to note that the absence of evidence of a conflict of interest does not necessarily guarantee the absence of any such conflict, and my review is limited to the information available through the authors' disclosures.

9) Other Sources of Bias

In my review, I identified that two of the studies, Leppert et al. (2019),[172] and Saunders et al. (2019),[155] had other sources of bias that could not be classified in one of the eight components reported above. The Leppert study was conducted to investigate the genetics of ASD and only marginally focused on

acetaminophen. Therefore, these two studies were scored as "high risk of bias". The Saunders study used matching in the study design, but did not account for it in the analysis, a situation that causes bias itself.[5]

My literature search identified six studies, which I rated based on the nine criteria. My review showed large differences in quality across these six studies. The study by Saunders et al. (2019),[155] scored poorly across many criteria; this was a retrospective study with minimal consideration of epidemiological methods, including confounding, selection of controls, and adjustment for confounders and matching variables. My average score across the nine criteria was 2.8, reflecting its poor quality. Similarly, Leppert et al. (2019),[172] scored poorly across multiple criteria. Based on my analysis across the nine criteria and my general concern about the lack of respect of basic tenets of epidemiology, I assigned an expert opinion score of -2 (Very low-quality study/flawed) due to the quality of these two studies.

ii. Grading Strength of Evidence of Each Study on Prenatal Acetaminophen and ASD

I rated each of the ASD studies for strength of evidence utilizing the approach outlined above. The results of my ranking are detailed in Appendix 1.

As recommended by the Navigation Guide, I used my expert judgement to determine the overall strength of evidence provided by each study. By using this approach, I evaluated the strength of evidence provided by each study thoroughly and comprehensively, enabling me to make informed decisions about the quality of evidence provided by each study, as follows:

1) Sample Size

Out of the four studies I considered, I scored two studies that had sample size >5,000 at +2, one with sample size between 1000-5000 at +1, and one sample size between 500-999 at 0. The largest single study (Liew, 2016) included 64,322 participants; the smallest study (Ji, 2020) included 996 participants. Alemany, 2021, which included six cohorts together in one combined analysis, had even a larger total size (N=73,881[4]).

[4] Only two of the six included cohorts had published results previously. Because the combined publications only included 9,160 of the 73,881 participants in the combined analysis, all three studies were included in my assessment.

2) Large Effect

I scored one study at +2 (relative risk >2), one study at +1 (relative risk between 1.5-2.0), and two studies at 0 (relative risk between 1.0-1.5 and statistically significant results). It is worth noting that that study that showed the largest effect was the one that used objective measurements of acetaminophen in cord blood to quantify the exposure. This finding suggests that the other three studies may be subject to measurement error in the classification of the exposure. This type of measurement error, because of the prospective design of all study, is expected to be independent of ASD outcomes and therefore bias the results toward the null. This suggests the other three studies report relative risks that are artificially low—and that the true risk is higher. It is worth noting that all the three studies I considered showed a statistically significant association linking prenatal acetaminophen with ASD.

3) Exposure-response Relationship

I scored two studies at +2 (evidence of an exposure-response relationship) and two studies at 0 (no evidence of an exposure-response relationship). It is worth noting that the two studies that provided no evidence of an exposure response-association did not report an exposure response analysis.

4) Internal Consistency

I scored four studies at +2.

5) Control of Bias

As I mentioned above, in the analysis of strength of evidence, I did not focus on two studies that resulted to be flawed when reviewed using the risk of bias analysis. The other studies used a variety of precautions and study designs that limited bias (e.g., prospective design, statistical analyses addressing confounding and loss to follow up, etc.). However, some types of bias, e.g., that due to measurement errors of the exposure and/or outcomes, are still possible. Therefore, I scored one study at +2 (very low risk of bias), because that study used objective measurements of the exposure in cord blood and also controlled for confounding by indication in the analysis. I scored the remaining three studies at +1 (low risk of bias); these studies provided solid control of bias and controlled by adjustment by indication. It is worth noting that the lack of objective measurement of acetaminophen levels in the three studies rated at +1 would bias the results toward the null, as discussed above.

6) Other Factors

There were no other factors that required an adjustment of the Strength of Evidence score.

c. Expert Opinion Score on the Overall Quality of Each Study on Prenatal Acetaminophen and ASD

I evaluated each of the ASD studies to determine an expert opinion score following the approach outlined above. The results of my ranking are detailed in Appendix 1.

Based on the sum of the scores across the six criteria, two studies had an initial overall score equal to +2 (very strong evidence) and two studies had an initial overall score equal to +1 (strong evidence). My review of the four studies did not identify any factor that would let me increase or decrease the final scores. Therefore, I adopted these scores above as my final opinion score on the strength of evidence provided by each study.

d. Final Determination Based on the Navigation Guide Analysis About the Toxicity of Prenatal Acetaminophen Use and Child's ASD

Using the above-described Navigation Guide approach, my final determination is that there is strong evidence of a causal link between prenatal acetaminophen use and an increased risk of being diagnosed with ASD in children. This determination is based on the review of six studies and the evaluation of four of them for strength. The studies consistently reported a positive association between prenatal acetaminophen use and ASD, with an exposure-response relationship observed in two of the three studies. The evidence is supported by the robust study designs and methods, large sample sizes, and control for potential sources of bias and confounding, including confounding by indication. Furthermore, the consistency and coherence of the findings across multiple studies strengthens the evidence of the association. My determination is also supported by strong evidence about plausible mechanisms linking prenatal acetaminophen exposure and child's ASD from experimental models.

Question addressed by the Navigation Guide analysis: can acetaminophen use during pregnancy cause ASD?

Final determination: Yes

Statement describing acetaminophen use during pregnancy in relation to child's ASD: Based on current evidence and my Navigation Guide Analysis, I

classify acetaminophen use during pregnancy as "Known to be Toxic" because of its ability to cause ASD in children.

e. Is Acetaminophen Use During Pregnancy Causally Associated with Other Neurodevelopmental Disorders?

i. Grading Risk of Bias of Each Study on Prenatal Acetaminophen and Other Neurodevelopmental Disorders

I rated each of the "other" studies for risk of bias utilizing the approach outlined above. The results of my ranking are detailed in the attached Appendix 1.

1) Selection

All studies I reviewed were prospective cohort studies where pregnant women were enrolled during pregnancy or at delivery and their children assessed prospectively for other NDDs, including behavioral difficulties, cognitive outcomes, executive function, psychomotor problems, lower communication skills, IQ, neurodevelopmental performance and development, and oppositional-defiant and conduct disorders. Therefore, in these studies all participants were enrolled—during pregnancy or shortly after delivery—regardless of their exposure to prenatal acetaminophen. Mother and child pairs were then followed up over time for many years and children were assessed to evaluate alterations in neurodevelopment. Therefore, there was no knowledge either at enrollment of their neurodevelopmental status. Because of their prospective nature, the studies were not typically susceptible to these sources of bias and therefore I rated nearly all studies at "low risk of bias". One study was rank as "probable high risk of bias" due to it being a case-control study.

2) Blinding

All the studies evaluated were prospective and therefore not subject to recall bias, except for one case control study. Therefore, I rated fourteen studies at low risk of bias (score = 1) and one study at probably low risk of bias (score =2.)

3) Exposure

One study directly measured acetaminophen in meconium. Because of the direct, objective measurements of acetaminophen, I rated this study at low risk of bias (score = 1). The other studies assessed acetaminophen use during pregnancy through questionnaires administered to the mothers either during pregnancy or shortly after delivery. I rated these studies at "probably low risk of bias"

(score = 2). However, my review identified two studies using maternal self-reports that appeared to have lower quality data. Parker et al. (2019),[205] was based on a study in which data used in this analysis were originally collected as part of a study of risk factors for and sequelae of a craniofacial malformation, particularly hemifacial microsomia. Controls were non-malformed children that were matched to cases on birth year and pediatric practice or practices within the same zip code. Standardized interviews were administered after delivery and prior to childhood neurodevelopmental assessments, therefore, memory bias may be affecting the results. Therefore, I rated this study at "probably high risk of bias" (score = 3). Tovo-Rodriguez et al. (2020),[169] reported no association between acetaminophen exposure and neurodevelopmental performance. However, the collection of data about acetaminophen exposure is very wide (perinatal period) and did not include dose. Therefore, it is highly likely that acetaminophen use was grossly underreported. Therefore, I rated this study at "probably high risk of bias" (score = 3). Overall, the average score across the 14 studies for exposure assessment was 2.0, which indicates probably low risk of bias overall. It is worth noting that because of the prospective nature of the studies, the misclassification of the exposure is expected to be unrelated to the outcome (i.e., non-differential). This type of misclassification is expected to dilute the signal, because some exposed mother-child pairs are classified as unexposed, and vice versa some unexposed mother-child pairs are classified as exposed. Therefore, I believe that the real magnitude of association to be higher than that reported by most studies. Indeed, the only study that used objective measurements of acetaminophen in cord blood or meconium showed no association with neurocognitive development but used a very limited sample size to determine associations. It is, therefore, likely that the use of maternal self-report attenuated the magnitude of relative risks estimated by the studies and that the actual effects are substantially stronger.

4) Outcomes

Based on the above criteria, I rated thirteen studies as "low risk of bias", one study at "probably low risk of bias", and one study at "probably high risk of bias".

5) Confounding

My review showed that most studies accurately evaluated potential confounders and used appropriate methods for adjusting for confounding variables. I rated twelve studies as "low risk of bias" and three studies as "probably low risk of bias". My decision to rate studies that did not control for confounding by indication at "probably low risk of bias" (score=2) was also supported by my review of the literature:

the studies that evaluated confounding by indication in the context of prenatal acetaminophen and abnormal neurodevelopment (e.g., ADHD) showed minimal differences after adjusting for confounding by indication relative to the estimates that did not adjust for this type of confounding. Therefore, these studies do not support the concept that confounding by indication is a relevant source of bias for the associations between prenatal acetaminophen and other NDDs.

6) Incomplete Data

The studies that I reviewed employed various methods to address incomplete data, such as imputation and multiple imputation of missing data. These methods allowed the researchers to make informed estimates of missing values, which can help to reduce bias in the study's findings. Furthermore, most of the studies reported that missing data were of low frequency, which suggests that the overall impact on the study's conclusions was likely minimal. Based on my review, I rated eight studies as having a "low risk of bias" with respect to incomplete data, meaning that they adequately addressed missing data and produced reliable results. Seven studies were rated as "probably low risk of bias," indicating that they likely addressed missing data appropriately, but with some limitations. Overall, by using appropriate methods such as imputation and multiple imputation, and reporting low frequency of missing data, these studies demonstrated a strong commitment to rigorous research methodology and high-quality data analysis.

6) Selective Reporting

In order to evaluate the reliability and validity of a research study, it is important to assess whether the study report appears to have selective outcome reporting. Selective outcome reporting occurs when the results that are reported in a study are biased due to the selective inclusion or exclusion of certain outcomes or data. Upon reviewing the studies, I found no evidence of selective outcome reporting across the studies. However, it is important to note that my evaluation was based solely on the information that was reported in each of the papers. It is possible that selective reporting may have occurred but was not apparent from the information that was presented.

7) Conflict of Interest

Based on my review of the studies, there was no evidence that the authors received support from a company, organization, or other entity having a financial interest related to the study questions. I specifically reviewed the funding or sponsorship of each study. However, it's important to note that the

absence of evidence of a conflict of interest does not necessarily guarantee the absence of any such conflict and my review is limited to the information available through the authors' disclosures.

8) Other Sources of Bias

In my review, eleven studies had no source of bias that was not otherwise accounted for in the analysis. Four studies had additional, unaccounted for bias include limited sample size and failure to adjust for confounding by indication.

9) Summary of Risk of Bias in Other Neurodevelopmental Disorders Studies

Upon reviewing the studies, I found that the average of my scores across all nine possible sources of bias was equal to 1.3, indicating that, on average, studies were appropriately conducted, and bias was well prevented and/or controlled in the studies. However, it is important to note that not all sources of bias carry equal weight. In some cases, a single source of bias can heavily influence the study results and conclusions. For this reason, the Navigation Guide recommends that experts review the quality of the studies. In order to account for potential limitations and weaknesses in the studies, I used my findings to downgrade the strength of evidence provided by studies that were deemed to be lower quality due to individual sources of bias that might weighted heavily on the results. This process was part of the "grading of the strength of evidence", as described in the next session.

By carefully evaluating potential sources of bias and downgrading studies based on their quality, I was able to provide a comprehensive assessment of the available evidence on the association between acetaminophen during pregnancy and risk of other NDDs. This approach allowed me to make more informed judgments about the reliability and validity of the studies, and to provide a rigorous analysis of the current state of evidence on this topic.

ii. Grading Strength of Evidence of Each Study on Prenatal Acetaminophen and Other Neurodevelopmental Disorders

I rated each of the other NDD studies for strength of evidence utilizing the approach outlined above. The results of my ranking are detailed in Appendix 1.

As recommended by the Navigation Guide, I used my expert judgement to determine the overall strength of evidence provided by each study. By using this approach, I evaluated the strength of evidence provided by each study thoroughly and comprehensively, enabling me to make informed decisions about the quality of evidence provided by each study, as follows:

1) Sample Size

I scored six studies that had sample size >5,000 at +2, five studies with sample size between 1000-5000 at +1, two studies with sample size between 500-999 at 0, and one with sample size between 250-499 at -1. No study had sample size <250, which would have called for a -2 score. The scoring distribution reflects the large sample size of most studies. The largest study, Skovlund et al. (2017),[185] included 58,410 participants. The smallest study, Laue et al. (2019),[3] included 188 participants.

2) Large Effect

I scored one study at +2 (relative risk >2), five studies at +1 (relative risk between 1.5-2.0), six studies at 0 (relative risk between 1.0-1.5 and statistically significant results), and three studies at -1 (non-statistically significant associations). No study qualified for the -2 score (significant association indicating that prenatal acetaminophen protects children against other NDDs). It is worth noting that most studies showed a statistically significant association linking prenatal acetaminophen with other NDDs and no study showed a protective association.

3) Exposure-response Relationship

I scored two studies at +2 (evidence of an exposure-response relationship), one study at +1, and twelve studies at 0 (no evidence of an exposure-response relationship). Most of the studies that provided no evidence of an exposure response association did not report an exposure response analysis, in some cases due to limited sample size that made such analysis not feasible.

4) Internal Consistency

I scored ten studies at +2 (findings with high degree of consistency), one study at +1 (moderate/medium consistency), four at 0 (moderate consistency), and none at -1 (some inconsistency or lack of clarity) or -2 (major inconsistency). Therefore, the large majority of the studies showed a high level of consistency.

5) Control of Bias

The risk of bias analysis above showed that most studies used a variety of precautions and study designs that limited bias (e.g., prospective design, statistical analyses addressing confounding and loss to follow up, etc.). This is expected in well-designed studies. If the study was well-designed and executed with very low risk potential sources of bias, I left the score at 0. Indeed, the studies used state of the art epidemiology techniques to address and correct bias. However, some types of bias, e.g., that due to

measurement errors of the exposure and/or outcomes, are still possible. Therefore, I scored only one study at +2 (very low risk of bias), because that study used objective measurements of the exposure in meconium and also controlled for confounding by indication in the analysis. I scored nine studies at +1 (low risk of bias); these studies provided solid control of bias and typically controlled by adjustment by indication. I scored three studies at 0 (moderate risk of bias) and two studies at -1 (high risk of bias). It is worth noting that except for confounding by indication, all the sources of bias I examined (e.g., overmatching, measurement error/misclassification of exposures or outcomes) would bias the results toward the null.

6) Other Factors

For all studies but one, I identified no other factors that could not be classified in one of the categories above. For one study (Laue, 2019), I decreased the strength score from 0 to -1 due to the very small sample size.

iii. Expert Opinion Score on the Overall Quality of Each Study on Prenatal Acetaminophen and Other Neurodevelopmental Disorders

I evaluated each of the other NDD studies to determine an expert opinion score following the approach outlined above. The results of my ranking are detailed in Appendix 1.

In conclusion, my expert opinion scores rated nine studies at +1 (strong evidence), five studies at 0 (moderate evidence), and one study at -1 (weak evidence).

iv. Final Determination Based on the Navigation Guide Analysis About the Toxicity of Prenatal Acetaminophen Use and Other Neurodevelopmental Disorders

Using this approach, my final determination is that there is strong evidence of an association between prenatal acetaminophen use and an increased risk of other NDDs in children. This determination is based on the evaluation of 15 studies, including nine high-quality studies that provided very strong evidence of an association. The studies consistently reported a positive association between prenatal acetaminophen use and other NDDs, with an exposure-response relationship observed in some of these studies. The evidence is supported by the robust study designs and methods, large sample sizes, and control for potential sources of bias and confounding. Furthermore, the consistency and coherence of the findings across multiple studies strengthens the evidence of the association. My determination is also supported by strong evidence about plausible mechanisms linking prenatal acetaminophen exposure and child's other NDDs from experimental models.

My final determination based on the Navigation Guide Analysis is the following:

> **Question addressed by the navigation guide analysis:** Can prenatal use of acetaminophen cause other NDDs?
>
> **Final determination:** Yes
>
> **Statement describing acetaminophen use during pregnancy in relation to child's other neurodevelopmental disorders:** Based on current evidence and my Navigation Guide Analysis, I classify acetaminophen use during pregnancy as "Known to be Toxic" because of its ability to cause other NDDs in children.

2. Bradford Hill Analysis – In Utero Acetaminophen Exposure and Neurodevelopmental Disorders

As Dr. Hollander explains in his report, and as is apparent from my own review of the literature, when reviewing the link between prenatal acetaminophen exposure and ADHD and ASD, it is appropriate to consider not only studies that assess ADHD and ASD specifically —which I have done in detail—but also studies that assess symptoms of NDDs that are consistent with ADHD and ASD. NDDs refer to a broad spectrum of conditions and symptoms caused by abnormal brain development. As a general matter, the NDDs covered by my assessment are those defined in the DSM-5 as a group of conditions with onset in the developmental period (*i.e.* childhood) with deficits that produce impairments of functioning.[59] These impairments include deficits in cognition, communication, motor skills, self-regulation, or social-emotional functioning. The symptoms associated with these disorders transcend diagnostic boundaries.

Recognizing this, [redacted] the FDA [redacted] considered studies that assessed NDD symptoms when assessing the causal relationship between prenatal use of acetaminophen and ADHD and ASD; as with my analysis, they did not limit their review to studies that strictly focused on ADHD and ASD.[206] [redacted] I join the approaches of the FDA [redacted] and review all of the studies detailed in Section G. of my report, and Appendix 1 —which include studies on ADHD specifically, studies on ASD specifically, and studies on NDD symptoms more generally—to undertake a Bradford Hill analysis to answer the questions of whether prenatal use of acetaminophen can cause ADHD and ASD. Based on my Bradford Hill analysis, I conclude, to a reasonable degree of medical, epidemiological, and scientific certainty, that prenatal use of acetaminophen is a cause of NDDs, including ADHD and ASD, in children.

a. Strength of Association

As explained above, and detailed in Appendix 1, observational studies have consistently found a statistically significant association between acetaminophen use during pregnancy and an increased risk of NDDs children. Even after adjustment for a large number of potential risk factors, these studies have continued to show statistically significant results. Although there is "no general rule for how large an association needs to be to meet this consideration,"[5] in many of the studies, the magnitude of the association was moderate, with risk ratios between 1.0 and 2.0.[1,11–13,18,167,168,171,180,183,185,186,191,192] Even though these studies show a moderate magnitude of association, the number of studies that have consistently found a statistically significant association weighs heavily in support of this factor. This factor also relates to consistency, which I discuss below.

Although the association in these studies is moderate, these results are nevertheless significantly stronger than other, known causal associations. The associations shown here are stronger than for other exposures "generally agreed to reflect causal effects," including the link between "air pollution and mortality," "smoking and heart disease," and "environmental tobacco smoke [*i.e.*, secondhand smoke] and lung cancer."[5] For this reason, Bradford Hill cautioned against "dismiss[ing]" a potentially causal association on the "grounds that the observed association appears to be slight" because "there are many occasions in medicine when this is in truth so."[6] For example, as detailed above, air pollution is a known risk factor for a number of diseases that cause death, including lung cancer and chronic obstructive pulmonary disease, cardiovascular disease, and dementia. And yet the best-designed epidemiology shows a relative risk of 1.06 (RR = 1.06, 95% CI = 1.05-1.07) for an increase of 100 µg/m3 increase in total particle concentrations in ambient air. The magnitude of the risks in these studies is substantially higher. Two other scientists recognized this when they said in a published article that "[g]iven a high prevalence and widespread use of acetaminophen, even of small magnitude with excess risk will have public health importance in this case. Just ignoring reported findings is unacceptable with the consequences at stake."[10]

Also, there is reason to believe that the magnitude of the risk in many of these studies has been dampened due to non-differential exposure misclassification resulting from the inability to directly measure acetaminophen exposure in many of the studies. In those studies, the researchers were forced to rely on self-reporting of acetaminophen use from the mothers themselves—likely biasing the risk estimates toward the null and artificially depressing the risk ratios. The best evidence of this effect comes from the studies where exposures were measured directly (via meconium and umbilical-cord

blood). In those studies—which were not forced to rely on maternal self-reporting alone—the strength of the association became quite large. In the Ji study, for example, children with the highest levels of acetaminophen measured in their umbilical cord plasma demonstrated a statistically significant ADHD and ASD odds ratio of 2.86 and 3.62, respectively. As the Consensus Statement authors noted, this is a "more than twofold [and threefold] higher odds of an ADHD [or ASD] diagnosis." That is undeniably a strong association.

Similarly, in the Baker study[4]—on which I was a co-author—the authors were also able to directly measure acetaminophen levels in the child's meconium. Compared to no acetaminophen, detection of acetaminophen in meconium was associated with increased odds of ADHD of 2.43, suggesting a 143% increase in risk. That is also a strong association. As the Consensus Statement authors noted, this "effect size" is a "large" one—so large, in fact that "residual confounding by uncontrolled factors is a less likely explanation for [the] identified associations."[2] As the study authors put it, this result (along with Ji) suggests that "prior studies may have been biased toward the null by inaccurate maternal recall" and that the real association is indeed as strong as Baker and Ji suggest. As my above analysis using the Navigation Guide makes clear, these studies—which are of extremely high quality—show a strong association between prenatal acetaminophen use and a child's likelihood of developing NDDs.

The classic Bradford Hill approach to evaluating strength considers only the magnitude of the risk ratio—and not the statistical significance—and my opinion is that this element is satisfied on that basis as explained above. Under more modern approaches to evaluating the Bradford Hill factors, however, researchers should also consider the statistical significance of results as well as their magnitude when evaluating strength. As one set of researchers recently put it, "[t]oday, statistical significance—not the magnitude of association—is the accepted benchmark for judging the strength of an observed association, and thus its potential causality."[32] And the strength of statistical significance is very high in these studies. For instance, the meta-analysis by Gou et al. (2019),[17] which included a total of 244,940 participants, reported a $p<0.00001$ for the association between prenatal acetaminophen and child's ADHD. In the Ji et al. (2020),[165] study, the study reported p-values of .08 and .002 for the associations between the second and third quartiles oaf acetaminophen levels in umbilical cord plasma and ASD diagnoses. There are numerous other examples: The vast majority of the studies discussed in detail above reported strongly statistically significant results with low p-values—including the meta-analyses. In my opinion, the strength criterion is satisfied here by the epidemiological studies.

b. Consistency

"A consistent finding is an association reported across multiple populations, over time, and using different study designs."[5] That is certainly the case here. As described in detail above, the association between prenatal acetaminophen exposure and NDDs in children has been observed in multiple studies—including extremely large cohort studies and meta-analyses—across many different time periods and patient populations. There are at least ten (10) studies showing a statistically significant association between prenatal acetaminophen use and ADHD. There are at least three (3) high-quality studies showing a statistically significant association between prenatal acetaminophen use and ASD. And there are at least five (5) high quality studies showing a statistically significant association between prenatal acetaminophen use and symptoms of NDDs.

As my analysis using the Navigation Guide makes clear, studies of high quality have consistently demonstrated a link between acetaminophen and NDDs (including ASD and ADHD). I am not alone in this belief. As a 2019 review put it—publishing before much of the more recent literature—the previous "seven studies have consistently suggested a moderately increased risk [of ADHD] from in utero acetaminophen exposure," lending "weight to the hypothesis that the association is causal."[17] A 2021 review noted that there has been a "consistent pattern of results . . . observed for the association between prenatal acetaminophen exposure and ADHD symptoms."[18] And the authors of the consensus statement note that a full 26 studies have "identified positive associations with APAP exposure during pregnancy and a range of clinically assessed and parent-reported neurodevelopmental outcomes, primarily attention deficit hyperactivity disorder (ADHD)."[2]

As explained above, there are some null results in the literature, *i.e.*, studies that did not show a statistically significant association between prenatal acetaminophen use and NDDs. But those studies are in the extreme minority—the vast majority of studies *did* show a statistically significant association. And in any event, it is "completely fallacious" to deem a set of studies "inconsistent simply because some results are 'statistically significant' and some or not."[5] A set of studies is still consistent even if some of the results are not statistically significant.

This consistency strengthens the argument that there is a true association between prenatal acetaminophen and NDDs. Though not "definitive," this "presence of a consistent result" is "a compelling argument for causality."[5] Indeed, nearly all studies published to date support this conclusion. For this reason, the authors of the Alemany study agree that the Bradford Hill consideration

for consistency has been satisfied for the link between acetaminophen and both ASD and ADHD. Specifically citing the original Bradford Hill address, they state that "consistency is supported because we observed consistent results using a variety of populations and methods."[18] The authors of the Bauer and Kriebel review agree as well, concluding that "there were consistent findings in the nine prospective cohort studies within five cohorts suggesting adverse neurodevelopmental outcomes in children following APAP use in pregnancy."[7] The same is true for the authors of the Olsen and Liew review, who noted that "five prospective cohorts" involving "a number of independent investigations" have "consistently estimated a positive link between maternal acetaminophen intake in pregnancy and a range of neurobehavioral outcomes in childhood."[10] In my opinion, the consistency element is strongly satisfied here.

c. Specificity

Specificity is satisfied when a disease is caused by essentially only one substance, as is the case for mesothelioma and asbestos, or when the exposure causes only one disease. This element in causality assessment is "widely considered weak or irrelevant from an epidemiologic standpoint."[32] This is because there are numerous well-known causal relationships that do not satisfy this criterion. As Bradford Hill pointed out, tobacco smoking does not exhibit "specificity" with respect to lung cancer—since smoking causes more diseases than just lung cancer, and some non-smokers develop lung cancers as well—but tobacco smoking is nevertheless recognized as being causally associated with lung cancer. That is why even Bradford Hill himself cautioned that "we must not, however, over-emphasize the importance of [specificity]."[6] Here, not every child who develops NDDs will have been exposed to Acetaminophen while in utero. The etiology of NDDs is multifactorial. But as Bradford Hill noted, this is often true of causal associations. "Indeed, many behavioral, environmental, social, and genetic risk factors have been linked to more than one health outcome," meaning that even in situations of known causality, specificity is not satisfied.[5] In my view, the specificity criterion is not satisfied here. However, it is generally considered by modern epidemiologists to be all but irrelevant.

d. Temporality

This criterion looks at whether exposure to a substance precedes onset of the disease, in particular whether there is any possibility of "reverse causation," whereby the outcome actually leads to the exposure.[5] The temporal relationship between in utero prenatal acetaminophen exposure and NDDs in the relevant studies is well established, with the exposure preceding the outcome. Indeed, most studies

evaluated were conducted prospectively, *i.e.*, women were enrolled during pregnancy or at delivery at the latest. Information about their use of acetaminophen was typically collected during pregnancy or at delivery. Children were then followed up over time, often with multiple assessments over the years. There is no suggestion in the literature that reverse causation is at work—nor could there be, given the fundamental nature of the relationship being examined. By the time the child is diagnosed with NDD(s), prenatal use has already occurred and cannot be influenced by that diagnosis. The authors of the Alemany study agree that this criterion has been satisfied for the link between Acetaminophen and ADHD and ASD. Again, specifically citing the original Bradford Hill address, they state that the "causal" element of "temporality" is "supported by the current findings."[18] In my opinion, the temporality element is satisfied here.

e. Biologic Gradient

This criterion (also referred to as dose response or exposure response) looks at whether an increase in exposure levels leads to an increase (or decrease) in the outcome of interest. Bradford Hill noted that "if a dose response is seen, it is more likely that the association is causal."[6] Here, virtually every study that was powered to evaluate, and did in fact evaluate, dose response found such an association between the number of days of prenatal acetaminophen use or its cumulative dose and NDDs in children. As of 2018, "in all six of the ADHD and ASD symptom studies that investigated the relationship," "there was evidence of a dose-response gradient of increased risk with increasing exposure."[7] Since then, the evidence of dose response has strengthened even further. Although one study did not show a dose response for the association between prenatal acetaminophen use and reduced IQ, the literature as a whole supports a dose response between prenatal acetaminophen use and NDDs.

I summarize the body of these results in Appendix 1. As reflected in those tables, six studies assessed dose response for ADHD (Baker 2022[204], Ji 2020[165], Ystrom 2017[11], Liew 2016[167], Avella-Garcia 2016[168], Liew 2014[9]), two studies assessed dose response for ASD (Ji 2020[165], Liew 2016[180]), and three studies assessed dose response for general neurodevelopment. (Inoue 2021[192], Rifas-Shinam 2020[189], Skovlund 2017[185]). In other words, in these studies, as the amount of acetaminophen that a pregnant woman consumed increased, so did the risk of the child developing NDDs. Notably, a clear dose response was seen in the two studies—Ji and Baker—that were able to directly measure acetaminophen levels, either in meconium or in umbilical cord plasma. As the level of in utero acetaminophen (measured directly) increased, so did the likelihood of the child developing ASD and ADHD.

This is compelling evidence in support of causation, as it is difficult to hypothesize other explanations for why this dose-response relationship would exist if the relationship were not causal, and the obvious confounders were controlled for in the studies themselves. In most studies, the dose-responses seen were monotonic—"wherein increased exposure results in increased incidence of the disease"—which provide "the clearest evidence of a causal relationship."[32] The authors of the Alemany study agree that this criterion has been satisfied for the link between Acetaminophen and ASD and ADHD. Again citing the original Bradford Hill address, they state that "previous studies have shown dose-response effects for both [autism spectrum condition] and ADHD symptoms."[18] Other authors have also explicitly stated that this criterion is satisfied.[7,17,209] In my opinion, the biologic gradient criterion is satisfied here. My opinion is further supported by the expert opinion of Dr. Louie.

f. Biologic Plausibility

This criterion looks at whether there is a biologically plausible mechanism by which the exposure can cause the outcome of interest. Although "what is biologically plausible depends on the biological knowledge of the day"—and thus this criterion cannot always be "demanded"[6]—here, there are several plausible biological mechanisms that could explain the association between prenatal acetaminophen exposure and NDDs in children. For example, prenatal acetaminophen exposure is known to create toxic metabolite NAPQI when it metabolized by CYP2E1 thereby causing oxidative stress in the fetal brain. Oxidative stress is a known pathway for the development of NDDs. Indeed, there are multiple such plausible mechanisms. The mechanisms of action that are likely to link prenatal acetaminophen to NDDs are detailed in Section E. The authors of the Alemany study agree that this criterion has been satisfied for the link between Acetaminophen and ASD and ADHD[18] as do Bauer and Kriebel in their 2018 analysis.[7] Again citing the original Bradford Hill address, the Alemany study authors state that the animal studies "provide biological plausibility" "for the current findings."[18] In my opinion, the biological plausibility criterion is satisfied here. My opinion is further supported by the expert opinions of Drs. Cabrera and Pearson.

g. Coherence

This criterion looks at whether a "cause-and-effect interpretation" of the data "seriously conflict[s] with the generally known facts of the natural history and biology of the disease."[6] There is no such conflict here. To the contrary, the association between prenatal acetaminophen exposure and ADHD and ASD in children is coherent with existing knowledge and understanding of the diseases and their causes.

Particularly, environmental factors are known to affect neurodevelopment, and pregnancy is widely considered a period of high susceptibility to environmental factors, as discussed in Section D.

Moreover, a causal association is coherent with the sudden and significant rise in the rates of NDDs seen over the past several decades. Bauer and Kriebel (2013)[209] found that "a country's average prenatal [acetaminophen] consumption was found to be correlated with its autism/ASD prevalence" with an R of 0.80—suggesting a strong correlation.[209] This is of course consistent with what one would expect if acetaminophen is indeed causally linked to NDDs. This is analogous to "[o]ne of the clues that led to the discovery of thalidomide as the causative agent of deformed limbs," namely that "[c]ountries with the greatest use of thalidomide by pregnant women during pregnancy were those with the highest incidence of deformed babies."[8] And more than one study author has suggested that widespread acetaminophen use might in fact be driving the increase in those rates, at least in part. For example, the authors of the Shaw paper stated that "the marked increase in the rate of autism [and] attention deficit disorder with hyperactivity may be largely caused by the marked increase in . . . the use of acetaminophen by pregnant women."[8] And the authors of the Liew et al. (2014) study stated that the observed association between in utero APAP exposure and ADHD "might explain some of the increasing incidence in HDK/ADHD" over the past decades."[9]

More than just the overall trend of increasing acetaminophen rates corresponding with increasing rates of NDDs, there is also some evidence that the rates have moved in tandem. For example, the following figure from Becker and Schultz[210] shows the ecologic relationship between ASD and events which altered acetaminophen sales in California:

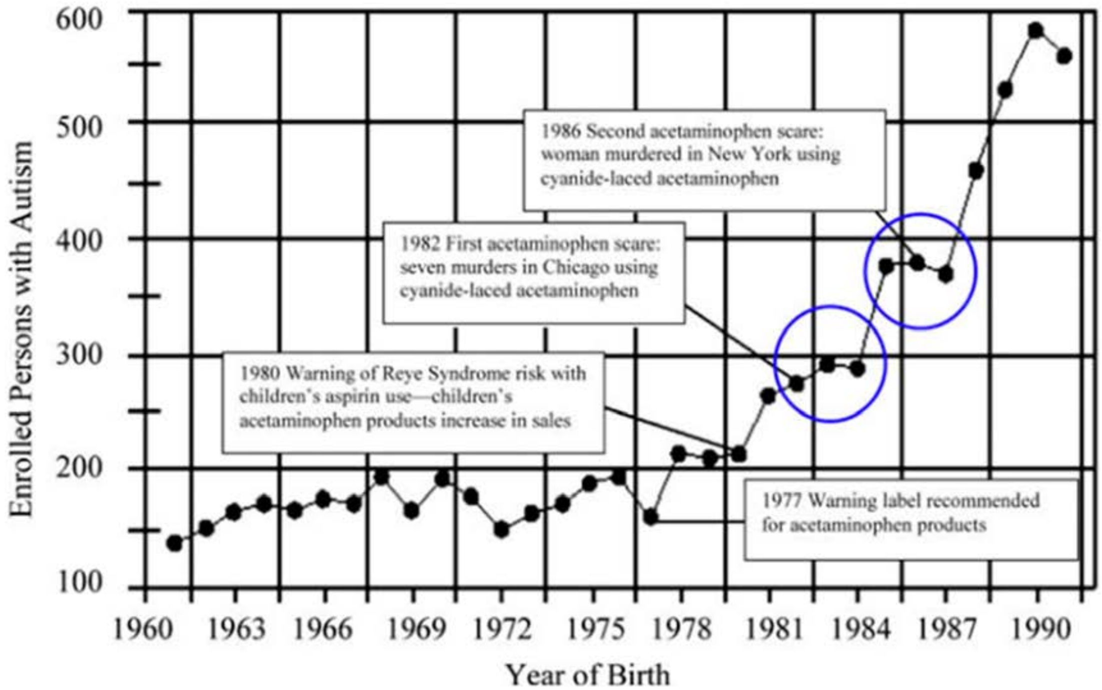


Fig. 1. Number of enrolled persons with autism in California by year of birth (adapted from: changes in the population of persons with autism and pervasive developmental disorders in California's developmental services system: 1987 through 1998. A report to the legislature (DDS, 1999). Fig. 1, P. 8. Available at: <http://www.dds.cahwnet.gov/Autism/docs/autism_report_1999.pdf>) with addition of events in the history of acetaminophen. The post-1982 and post-1986 downward inflections are circled.

This is analogous to Bradford Hill's own example of coherence, which was "the temporal rise" in both smoking rates and lung cancer rates during the 20th century.[6] The results of the observational studies described above are also consistent with the experimental evidence suggesting a mechanistic pathway by which acetaminophen causes NDDs. The authors of the Alemany study agree that this criterion has been satisfied for the link between Acetaminophen and ASD and ADHD.[18] Again citing the original Bradford Hill address, they state that the animal studies plus their own findings establish "coherence" "for the current findings."[18] In my opinion, the coherence criterion is satisfied here.

h. Experiment

"Occasionally it is possible to appeal to experimental, or semi-experimental evidence."[6] Here, ethical considerations preclude conducting experimental studies in humans—because of the risk of harming the developing fetus. Bradford Hill used this element typically to refer to "epidemiologic studies in disease risk declines following an intervention or cessation of exposure."[32] In his conception, "experiment" meant evidence "obtained from reducing or eliminating a supposedly harmful exposure and seeing if the frequency of disease subsequently declines."[5] Examples he gave were implementing dust reducing technologies for dust believed to be carcinogenic or employing safer lubricating fluids. One could argue that the ecologic data shown above satisfies Hill's semi-experimental evidence elements as it shows both increases in ASD rates when the use of acetaminophen goes up and reduced rates when use of acetaminophen is reduced. But under more modern approaches to evaluating the Bradford Hill elements, researchers are instructed to look not just at human experiments but animal, toxicologic, and epigenetic experiments as well. In particular, researchers can rely on "in vitro studies that test mechanistic pathways and demonstrate the biological role of an agent in disease progression."[32] And "[e]xperimental evidence can refer to clinical trials, to animal experiments, or to experiments on tissues."[5] Evidence from these studies is reported in Section E. And under that conception of the experiment criterion, it is entirely satisfied. Based on this more modern approach, my opinion is that this criterion is satisfied.

i. Analogy

This element looks to whether similar drugs have been shown to cause the outcome of interest. For example, as Bradford Hill notes, given that thalidomide was shown to cause defects in pregnancy, researchers should be willing to accept causation for "another drug" used in pregnancy based on "slighter but similar evidence."[6] And as the Rothman textbook notes, "based on what is known about the health effects of cigarette smoking, we might expect that inhalation of other combustibles (*e.g.* marijuana) would have similar effects, even in the absence of studies on the subject."[5]

Although "a lack of analogy does not preclude causation,"[32] and does not imply the "falsity of the hypothesis,"[5] there are nevertheless analogies here for other drugs. The FDA-approved label for Depakote, another drug previously used by pregnant women, for example, states that "the weight of the evidence supports a causal association between valproate exposure in utero and subsequent adverse effects on neurodevelopment, including increases in autism spectrum disorders and attention

deficit/hyperactivity disorder (ADHD)."[135] Valproic acid, like acetaminophen, has been shown to increase oxidative stress and deplete glutathione levels. This is one of the mechanisms by which Depakote is believed to cause NDDs. Accordingly, the analogy element is satisfied.

j. Method For Assessment of Bradford-Hill Elements:

My assessment of each study can be found in my Navigation Guide tables and analysis. In evaluating the strength of causality under Bradford-Hill, I first assess whether temporality is met. If it is clear that the disease preceded the exposure, then causality is not possible, and no further analysis is required. In some cases, temporality is unclear and the evidence for and against must be considered. In this case, temporality is clearly met: the women took acetaminophen while their children were *in utero*, long before those children were diagnosed with ADHD and ASD. While a lack of temporality precludes causation, a clear finding of temporality generally does not weigh significantly in favor of causation. In this case temporality is clearly met, but I assigned this element virtually no weight in assessing causality, since this element is so often satisfied.

Specificity, when met, should be given great weight in favor of causation. As explained above, however, when the specificity element is not met it should be given virtually no weight against a causal inference as there are very few known causal associations that satisfy the specificity element. This is particularly true in evaluations like the one being considered where both the mechanism(s) of action and the etiology of the injury are believed to be diffuse. In this case, specificity was not met, and in my analysis, this did not weigh against finding a causal association, since there are many known causal relationships where specificity is not satisfied.

Biologic plausibility can vary tremendously in influence from hypothesized mechanisms to very elegant animal studies demonstrating the biologic mechanisms of causation to human studies that unequivocally revealing the mechanism of causation. The evidence of biologic plausibility in this case is moderate to strong. The proposed mechanisms of action in this largely have been shown in both human and animal models. I have given biologic plausibility moderate weight in favor of causality.

As discussed above, there were multiple studies showing a dose response relationship (biologic gradient) between in utero exposure and NDDs. I agree with Bradford-Hill that such a finding "adds a very great deal" in favor of causality. The fact that there were studies with objective measures of exposure that showed clear dose response was a significant contribution to my assessment of causality. I weighed dose response strongly in favor of causation.

Strength of association is always considered an important factor in assessing causality. I, along with other researchers, have noted that the strength of association reported in most acetaminophen studies reviewed likely underestimates the risk of in utero acetaminophen exposure and neurologic developmental disorders. Additionally, because of the number of consistent outcomes and the various study designs that have enabled analyses to rule out bias, confounding and chance as explanations for the observed association, I find the strength of association to weigh heavily in favor of causation. Additional support in favor of this determination is that the studies that use objective measures of exposure demonstrate both biologic gradient and risk estimates that are more than double.

As for consistency, the increased risk of in utero acetaminophen exposure and the development of ASD, ADHD or symptoms consistent with those disorders was seen very consistently across many different study designs and populations. As Bradford-Hill explained, "whether chance is the explanation or whether a true hazard has been revealed may sometimes be answered only by a repetition of the circumstances and observations".[6] We now have additional statistical techniques to assess whether our outcomes are a matter of chance, but like Bradford-Hill, "I would myself put a good deal of weight upon similar results reached in different ways…"[6] Because we have both a variety of studies with varying neurodevelopmental damage end-points and a variety of study designs and populations – all with a tremendous degree of consistency among the studies – I gave consistency a great deal of weight in favor of causality.

As for coherence, a causality finding in this case presents no conflicts "with the generally known facts of the natural history and biology" of the injury in question.[6] Additionally, as noted above, causality in this case is coherent with the relevant ecologic data. While I find the coherence element is met in this case, I give it only a minor weight in favor of causality because the injury in question is believed to have many causes and possibly many pathways of injury.

While we do not have the traditional experimental evidence envisioned by Bradford-Hill, we have analogous evidence with the sudden increased and decreased use of acetaminophen at various points in time and the parallel prevalence of ASD and ADHD. We also have the experimental evidence generated from the animal studies and more basic lab science. Although compelling, in this case I view this element merely corroborating evidence of causality and, therefore, I give it minimal weight.

As for analogy, as noted above, there are close fit analogies to the issue I address in this report. The analogy element, when met, makes one "ready to accept slighter but similar evidence with another drug

or another viral disease in pregnancy."[6] I agree with Bradford-Hill in that analogy makes a causal finding more acceptable, and the analogy element is satisfied here. I, however, place very little weight on this factor. Placing too much weight on this factor would promote spurious associations as causal – because sometimes analogous drugs do not have analogous effects – and would also ignore truly causal association when no analogy was available.

k. Conclusion based on Bradford-Hill Analysis

Every Bradford Hill element other than specificity, which Bradford Hill himself makes clear will seldom be met even in known causal associations, is met with respect to the association between in utero acetaminophen exposure and NDDs in offspring. My analysis of the Bradford Hill elements leads to the inescapable conclusion that prenatal use of acetaminophen exposure can cause the offspring to develop NDDs such as ADHD and ASD, as well as symptoms consistent with those diagnoses. I performed a Bradford-Hill assessment separately for ASD, ADHD and the constellation of neurologic deficits identified in my Navigation Guide assessment. For all of those injuries, I reach the same conclusion: the association between them and in utero acetaminophen exposure is causal. I hold each of these opinions to a reasonable degree of medical, epidemiological, and scientific certainly.

I recognize and consider that individual authors of the studies I reviewed did not make a causal determination and that some (though not all) cautioned against a causal inference. I identified many of these authors' limitations in my review of the epidemiological literature, Section G. It should be noted that epidemiologists rarely make a scientific finding of causation in a single study. Significantly, the authors of most of the individual studies did not consider the totality of the evidence as I did in my review but were focused on their individual results. And the totality of the evidence, along with my Bradford Hill analysis and my Navigation Guide analyses, shows that it is more likely than not that acetaminophen causes the NDDs of ADHD and ASD.

In addition, some of these authors suggest that their results should be read with caution due to possible confounders. But it is highly unlikely that confounding can explain away these strong, repeatedly observed associations between prenatal acetaminophen use and NDDs. As I detail in Section F.3.d., and in my Navigation Guide analyses, many of the authors structured their studies to account for an enormous variety of plausible confounders. And yet the association has persisted. In addition to those controls—which alone provide compelling evidence against confounding—many of the studies employed sophisticated epidemiological methods designed to examine whether residual confounding

might be driving the associations. The weight of those studies also suggest that this association is not due to confounding. (See Section G.4. above.) That is why so many of the study authors have made clear their view that bias (such as confounding) and chance are simply not likely explanations for this association.[10,17,20,22,209] Having ruled out confounding—and with chance simply not being possible given the consistency of these results—causation remains as the most likely explanation. Despite numerous attempts to "make the association go away," it has not.[10] Causation is all that remains.

Given the breadth of indications for APAP in pregnancy, and given the statistical signal picked up in many studies despite a great deal of "noise" in the data (biases that run towards the null), any theoretical confounder associated with consuming APAP would have to have enormous power in order to explain the association. While the makers of Tylenol have suggested that fever or other maternal infection may be the explanation, the relative risk of those conditions perturbing neurodevelopment combined with the relatively low number of women taking APAP for those conditions while pregnant—8% of women take for fever according to one study[16]—means that the mathematics simply do not add up. The in vivo mechanism studies, as well as the lack of relationship seen between neurodevelopmental outcomes with NSAID use, further validates this point. As two authors observed in response to the common refrain regarding confounding in these studies, "[t]he claims that these findings are due to 'confounding by indication' should be supported by evidence, not just opinions."[10] But there is simply no evidence that some kind of residual confounding – by indication or otherwise – can explain these repeatedly observed associations.

Two other analyses that invoked the Bradford Hill factors concluded that women should be cautioned against using acetaminophen while pregnant based on the epidemiological evidence. In one analysis that assessed Bradford Hill, Bauer et al. (2018), the authors concluded that "[t]here were consistent findings in the nine prospective cohort studies within five cohorts suggesting adverse neurodevelopmental outcomes in children following APAP use in pregnancy", therefore "[p]regnant women should be cautioned against indiscriminate use of this medication."[7] Similarly, authors of a 2021 review, Alemany et al. (2021) concluded that "[c]onsidering all evidences on acetaminophen use and neurodevelopment, we agree with previous recommendations indicating that while acetaminophen should not be suppressed in pregnant women or children, it should be used only when necessary."[18]

The FDA has reviewed some of the studies and noted that some studies are strong but also note, in their view, the purported weaknesses of some studies. Given the body of epidemiological evidence, the FDA recognized that further epidemiological studies would be unlikely to inform the causal question, but

suggested preclinical studies may be more informative on this issue.[211] Although I disagree with some of the FDA's conclusions regarding the underlying science, even the epidemiologists at the FDA agree with me that it is necessary to warn women that prenatal use during pregnancy must be "used judiciously" and to warn of the "possibility of neurodevelopmental harm."[212]

Other scientists have come to similar conclusions. For instance, Drs. Liew and Olsen published that "we believe time has for some precautionary action. Mothers to be should at least be advised to avoid the drug if treatment is not necessarily for her conditions."[10] [redacted] In short, I am not alone in my conclusion that acetaminophen can cause the NDDs of ASD and ADHD, thereby warranting a warning to pregnant women.

3. Sufficient Duration Required to Detect a Statistically Significant Increased Risk

As noted above, there is ample evidence of dose response, *i.e.*, there is ample evidence demonstrating that, as the amount of acetaminophen ingested by a pregnant woman increases, the risk of having a child with NDDs such as ADHD and ASD increases as well. A related, but conceptually distinct question is what amount of acetaminophen exposure has been shown to cause ADHD and ASD via the human epidemiology alone. Note that this question is also conceptually distinct from whether there is a threshold dose, *i.e.*, a minimum amount of acetaminophen exposure below which there is no increased risk at all. The studies reviewed above were not designed to determine the minimum exposure required for acetaminophen to cause NDDs, nor would it be practical to do so.

Based on my review of the human epidemiology literature, it is clear that 28 days or more of prenatal acetaminophen use has been shown to be sufficient to generate a statistically significant increase in risk of signs and symptoms of ADHD at the population level that is detectable in the human epidemiology employed thus far.[11,14,173] In these studies, women who took acetaminophen for 28 days or more while pregnant had a statistically elevated risk of having a child with ADHD. This is a conservative estimate.

Based on my review of the human epidemiology literature, it is clear that generally 28 days or more of prenatal acetaminophen use is sufficient to generate a statistically significant increase in risk of signs

and symptoms of ASD at the population level that detectable in the human epidemiology employed thus far.[14,180] In this study, women who took acetaminophen for 28 days or more while pregnant had a statistically elevated risk of having a child with ASD. This, too, is a conservative estimate.

This analysis should not be interpreted as endorsing the view that 27 days of acetaminophen exposure carries with it no risk. It is simply a recognition that 28 days or more has been demonstrated to lead to a detectable, statistically significant increased risk in the human epidemiology. This is also not to say that lower doses of acetaminophen do not increase the risk or are not causally associated with ADHD and ASD. Many studies have shown dose-response relationship between prenatal acetaminophen use and ADHD or ASD[9,11,180] and it is not clear whether there exists *any* threshold dose below which there is no risk at all. Moreover, many studies have found statistically significant elevations in risk associated with fewer than 28 days of exposure in certain populations, in some cases in as few as 1 week of exposure for ADHD and 2-5 weeks of exposure for ASD.[9,11,139,180] And even women who take acetaminophen for time periods shorter than those described above may well be at an increased risk. The study designs employed in the human epidemiology preclude more granular conclusions of whether even lower doses might lead to a statistically significant effect detectable at the population level. But it is abundantly clear that generally 28 days or more is a sufficient amount of time to cause a statistically increased risk for ADHD and ASD.

I. CONCLUSION

Numerous studies have shown a strong, statistically significant association between prenatal acetaminophen exposure and ADHD or ASD. Time and again, when researchers have looked at the data, they revealed that women who took acetaminophen while pregnant had a higher risk of having children with NDDs, including ADHD or ASD.

The studies showing this association are well-designed, as evidenced by the Navigation Guide analysis I performed. The studies have controlled for a vast array of potential confounders that might plausibly explain away the association, and yet the association has persisted nevertheless; even after the controls, women who took acetaminophen while pregnant still had a higher risk of having children with ADHD or ASD. More recent, innovative techniques have attempted to determine whether unmeasured and residual sources of confounding might be driving the association, and yet the association has again persisted. Multiple sets of study authors have made clear their views that “confounding alone is an unlikely explanation for the associations reported in these studies,”[17,18,20] leaving causation as the most

likely one. Despite all attempts to provide evidence of alternative explanations other than causation, the research has not been able to “make the association go away.”[10] As Bradford Hill wrote, even when an association is “new to science” or just “too odd,” when all other possibilities have been eliminated, “whatever remains, however improbable, must be the truth.”[6] At this point, all realistic sources of confounding have been eliminated, either by direct controls or more sophisticated study designs. Nevertheless, across different time periods, across different data sets, across different patient populations, the results have been terrifyingly consistent: when a mother takes acetaminophen while pregnant, the odds of her child having ADHD or ASD increase significantly. Causation is what “remains” as by far the most likely explanation.

After applying the standard Bradford Hill analysis, my opinion is that this association is indeed causal. All of the Bradford Hill elements of causation except one (specificity) are satisfied, and that element is singularly viewed as unnecessary and indeed unhelpful by modern epidemiologists. This is powerful evidence of causation. Multiple independent study authors have suggested the same thing, with one paper in particular specifically noting that five of the Bradford Hill elements – consistency , temporality, coherence, dose response, and biological plausibility—have all been satisfied.[18] A causal relationship is eminently plausible in light of acetaminophen’s demonstrated ability to affect the developing fetus. And a causal relationship is entirely consistent with one of the great epidemiological mysteries of the last 50 years: why have the rates of ASD and ADHD have gone up by thousands of percent in such a short period of time? Indeed, more than one author has stated that the “the marked increase in the rate of autism [and] attention deficit disorder with hyperactivity throughout much of the world may be largely caused by the marked increase in the use of acetaminophen by pregnant women.”[8,9] In light of the existing science, that explanation is tragic but unfortunately it is the most likely one.

This opinion is based on my extensive review of the medical and scientific literature, my own independent classification of the data based the standardized Navigation Guide approach, my application of the traditional Bradford Hill factors, and my experience and expertise in the areas of epidemiology and toxicology, including acetaminophen use and its effects on neurodevelopment. All opinions are made to a reasonable degree of medical, epidemiological, and scientific certainty. I reserve the right to amend or supplement this report as new information becomes available.

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[redacted]

The foregoing opinions are substantively identical to the opinions stated in my June 16, 2023 report. All opinions offered herein are held to a reasonable degree of scientific and medical certainty.

Dated: June 23, 2023

Respectfully submitted,

Andrea Baccarelli, MD, PhD, MPH

PMID	Author	1. Selection: Was the strategy for recruiting participants consistent across study groups?	2. Blinding: Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?	3. Exposure: Were exposure assessment methods lacking accuracy?	4. Outcomes: Were outcome assessment methods lacking accuracy?	5. Confounding: Was potential confounding inadequately incorporated?	6. Were incomplete outcome data inadequately addressed?	7. Does the study report appear to have selective outcome reporting?	8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?	9. Did the study appear to have other problems that could put it at a risk of bias?	AVERAGE	Notes
36170224	Sznajder,2022	1	1	2	2	2	1	1	1	1	**1.3**	Outcomes assessed at age 3 when ADHD symptomes may not be apparent yet in most future cases. Fever not included as a confounder due to exposure collinearity
32986124	Baker, 2022	1	1	1	1	1	1	1	1	1	**1.0**	Major strenghts in addressing bias due to special objective masures of exposure (meconium) and outcome (brain MRI). Limitation: The relatively small sample size is fully compensated by the added precision of meconium and brain MRI measurements
34046850	Alemany, 2021	1	1	2	1	1	1	1	1	1	**1.1**	This study included five cohort. Some differences between cohorts were noted.
31664451	Ji, 2020	1	1	1	1	1	1	1	1	1	**1.0**	Major strenghts in addressing bias due to objective masures of exposure in cord blood
31509360	Chen, 2019	3	1	2	1	2	1	1	1	1	**1.4**	The description of the logistic regression models does not specify whether only some or all of the matching variables were included as covariates, hence raising concerns about overmatching of controls. No assessment of confounding by indication.
30923825	Liew, 2019	1	1	2	2	1	2	1	1	1	**1.3**	Exposure was not recorded as occuring in pregnancy, but as regular use in the same year of the pregnancy. However, restricting the analysies to women who were pregnant at the time they provided medication use info did not change the results (slightly stronger association).

PMID	Author	1. Selection: Was the strategy for recruiting participants consistent across study groups?	2. Blinding: Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?	3. Exposure: Were exposure assessment methods lacking accuracy?	4. Outcomes: Were outcome assessment methods lacking accuracy?	5. Confounding: Was potential confounding inadequately incorporated?	6. Were incomplete outcome data inadequately addressed?	7. Does the study report appear to have selective outcome reporting?	8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?	9. Did the study appear to have other problems that could put it at a risk of bias?	AVERAGE	Notes
30458756	Tovo-Rodrigues, 2018	1	1	4	2	2	2	1	1	1	**1.7**	The authors cautioned that the proportion of reported acetaminophen use during pregnancy was much lower than expected (27% vs. 51% expected based on other independent data in the region). SDQ was used to assess the outcome, a test with high negative but low positive predictive value, hence potentially missing many ADHD cases. Both limitations are likely to have diluted the effects, resulting in a weaker association
28031314	Liew, 2016	1	1	2	1	1	1	1	1	1	**1.1**	
27353198	Avella-Garcia, 2016	1	1	2	2	1	1	1	1	1	**1.2**	ADHD evaluated at 4.8 years in average when most cases are harder to detect

PMID	Author	1. Selection: Was the strategy for recruiting participants consistent across study groups?	2. Blinding: Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?	3. Exposure: Were exposure assessment methods lacking accuracy?	4. Outcomes: Were outcome assessment methods lacking accuracy?	5. Confounding: Was potential confounding inadequately incorporated?	6. Were incomplete outcome data inadequately addressed?	7. Does the study report appear to have selective outcome reporting?	8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?	9. Did the study appear to have other problems that could put it at a risk of bias?	AVERAGE	Notes
27533796	Stergiakouli , 2016	1	1	2	2	1	1	1	1	1	**1.2**	ADHD was evaluated using the Strengths and Difficulties Questionnaire (SDQ), SDQ has high negative but low positive predictive value, hence potentially missing many ADHD cases. This limitation is likely to have diluted the effects, resulting in a weaker association
25251831	Thompson, 2014	1	1	2	2	1	2	1	1	1	**1.3**	ADHD was evaluated using the Strengths and Difficulties Questionnaire (SDQ), a proxy for ADHD diagnosis
24566677	Liew, 2014	1	1	2	1	1	1	1	1	1	**1.1**	Telephone based interviews.
3603404	Streissguth, 1987	1	1	2	3	2	1	1	1	1	**1.4**	Test for attention is not standard
Not in Pubmed	Gustavson, 2021 (Overal Study)	1	1	2	2	1	2	1	2	1	**1.4**	The second author (Ystrom) is Joint Editor for the joiurnal where it was published (a clear COI).
Not in Pubmed	Gustavson, 2021 (Sibling controlled study)	1	1	2	2	4	2	1	2	1	**1.8**	The second author (Ystrom) is Joint Editor for the joiurnal where it was published (a clear COI).

Source: The Navigation Guide to Assess Risk of Bias in Toxicology and Environmental Health Studies
https://guides.himmelfarb.gwu.edu/systematic_review/reporting-quality-risk-of-bias

1 Low Risk of Bias
2 Probably Low Risk of Bias
3 Probably High Risk of Bias
4 High Risk of Bias
NA Not applicable

PMID	Author, Year	A. Size	b. Large Effect (>2)	c. Dose Response	d. Internal consistency	e. Control of bias	f. Other	Average of criteria	Sum of criteria	Strenght of Evidence	Expert opinion score on study quality	Notes
36170224	Sznajder, 2022	1	0	0	0	1	NA	0.4	2	0	0	
32986124	Baker, 2022	-1	2	2	2	2	2	1.5	9	2	2	f. Brain MRI and measurement in meconium
34046850	Alemany, 2021	2	1	0	1	1	NA	1	5	1	1	
31664451	Ji, 2020	0	2	2	1	2	2	1.5	9	2	2	e. stratification by fever; f. measurements in cord blood
31509360	Chen, 2019	2	0	0	2	-1	NA	0.6	3	1	1	
30923825	Liew, 2019	1	0	0	2	0	NA	0.6	3	1	2	Higher opinion score because of stronger evidence from negative control exposure analysis
30458756	Tovo-Rodirgues, 2018	1	0	0	1	-2	NA	0	0	0	0	Opinion score driven by probable acetaminophen use underereporting. Strength of evidence driven by retrospective assessment of prenatal acetaminophen and probable underereporting
28031314	Liew, 2016	1	2	2	2	1	NA	1.6	8	2	2	
27353198	Avella-Garcia, 2016	1	1	2	2	1	NA	1.4	7	1	0	a. Younger age of children compared to other studies; Opinion score driven by young age of children (4.8 years), when ADHD may not have yet manifested itself
27533796	Stergiakouli , 2016	2	0	0	2	1	NA	1	5	1	1	Opinion based score lower than the maximum due to the use of the SDQ score as a proxy for ADHD diagnosis. N.B.: Bias likely toward the null
25251831	Thompson, 2014	0	-1	0	1	1	NA	0.2	1	0	0	Opinion score driven by small sample size with use of continuous scores
24566677	Liew, 2014	2	0	2	2	0	NA	1.2	6	1	1	e. telephone based interview assessing 40 types of drugs; potential for non differential misreporting; possible bias toward the null
3603404	Streissguth, 1987	-1	-1	0	-1	0	NA	-0.6	-3	-1	-1	Opinion score driven by small sample size and use of non standard attention score.
Not in Pubmed	Gustavson, 2021 (Overal Study)	2	2	0	1	2	-1	1.0	6	1	1	F. Ystrom is a joint editor in the journal that published the paper, presenting some concern about independent editorial decisions
Not in Pubmed	Gustavson, 2021 (Sibling controlled study)	-1	0	0	2	-2	-1	-0.3	-2	0	-1	e. Risk of confounding reflects that the sibling controls, while intended by the authors to control for unmeasured confounders, also eliminates the effect mediated by intermediate variables hence likely biasing the results toward the null. F. Ystrom is a joint editor in the journal that published the paper, presenting some concern about independent editorial decisions. Expert opinion score downgraded to -1 due to concerns about the very small effective sample size and the bias toward the null likely introduced by the elimination of the effects of intermediate factors.

Table - Grading of Strength of Each Study

Score	Study of Evidence
+2	Very Strong
+1	Strong
0	Moderate
-1	Weak
-2	Very weak/none

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
36170224	Sznajder, 2022	Pennsylvania, USA	Births: 2009-2011	OR=1.21 (1.01-1.45)	Prospective cohort	N=2400	Individual mean imputation of missing outcomes measures (<2%)	Nulliparous pregnant women in the third trimester, 18 to 35 years, English or Spanish speaking, planning to deliver at a hospital in Pennsylvania, no plans for the child to be adopted, and delivering at 34 weeks gestation or later.	Self reports of medication use during pregnancy in third trimester phone inteview. Dose and frequency were queried but not used in the analysis.	Attention problems from the Child Behavior Checklist (CBCL) at age 3 years (>80th percentile of the scale)	**Variable selection:** Variables associated with exposure and outcome. **Indication:** Infection, other indication variables did not meet the selection criteria **Other variables:** trouble sleeping, thyroid conditions, maternal age, insurance coverage, alcohol, anxiety/depression, stress. **Variable evaluated but not adjusted for** (see variable selection critierion above): Muscle pain, headache/migrane, cold/allergies, race, other non-prescription drugs, BMI, labor induction, mode of delivery, dystocia, antpartum bleeding **Not adjusted for due to collinearity:** fever	
32986124	Baker, 2022	Sherbrooke, Canada	Births: 2008-2010	OR=2.43 (95%CI: 1.41-4.21) Dose response: 10% higher odds for each doubling in acetaminophen in meconium	Prospective cohort	N=345	Missing covariate data were imputed with the median of continuous variables and the mode of categorical variables.	Women 18 years or older with no known thyroid disease	Measurement of acetaminophen in meconium samples	Parent-reported physician diagnosis of ADHD or diagnosis from medican records at 6-7 years of age.	**Variable selection:** a priori **Indication:** Used Inverse Probability Weights for variables that make more likely to use acetaminophen; this can help address confounding by indication; sensitivity analysis showed no differences when excluding possible indications. **Other variables:** child sex, familial income, and maternal characteristics, including age at delivery, education, prepregnancy body mass index, smoking during pregnancy , and alcohol use during pregnancy. Added maternal ADHD in sensitivity analysis	Objective measurements of fetal exposure to acetaminophen in meconium. Functional brain MRI performed to identify objective brain function alteractions associated with prenatal acetaminophen.
34046850	Alemany, 2021	United Kingdom, the Netherlands, Denmark, Italy, Spain, and Greece	Pregnancies: 1991-2008	OR = 1.21, 95% CI 1.07–1.36	Prospective Cohorts	N=73,881	Used cohort-specific criteria	Mother-Children with available data on either prenatal or postnatal exposure to acetaminophen and at least one outcome (ADHD or ASD)	Mothers were interviewed 2-4 times during pregnancy using standardized questionnaires.	Subscale of the CBCL11⁄2-5 and CBCL6/18 and the ADHD Criteria of DSM-IV (DSM-ADHD Questionnaire)	**Variable selection:** a priori **Indication: F**ever and infection during pregnancies. **Other variables:** Maternal and child covariates: age at delivery (years), education (low, medium, high), pre-pregnancy body-mass index (BMI), alcohol (yes/no), smoking (yes/no) and men- tal health problems (yes/no) during pregnancy, age at birth (years) and parity (nulliparous, > 1 and > 2), during pregnancy; sex, age at behavioral assessment (years), cold (yes/no) and respiratory infections (yes/no) in the first 2 years of life.	The exposure was assessed using maternal questionnaires or interviews. <u>N.B.:</u> This paper presents a combined analysis of 6 cohort studies in Europe. Two of them had reported results in other previous publications (Avella Garcia, 2016; Stergiakouli 2016). However, these two cohorts amounted to just approximately 10% of the entire sample size of this new combined study, which was therefore considered as including predominantly new original data.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
31664451	Ji, 2020	Boston, MA	Births: 1998-	Reference: Lowest tertile 2nd tertile: OR 2.26 (95% CI, 1.40-3.69) 3rd tertile: OR 2.86 (95% CI, 1.77-4.67)	Prospective cohort	N=996	Missing data for sociodemographic characteristics (<4%) imputed using multiple imputation by chained equations (MICE) with the Predictive Mean Matching method	Mothers who delivered singleton live births at Boston Medical Center (BMC), excluding conception via in vitro fertilization, deliveries induced by maternal trauma, or newborns with major birth defects.	Measurement of acetaminophen in cord blood samples (Fetal blood)	Diagnosis from Electronic medical records through 9.8 years of age in average	**Variable selection:** a priori, variables associated with exposure and outcome. **Indication:** stratified analyses by fever showed no differences between strata **Other variables:** maternal and child variables: maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, and low birth weight.	Objective measurements of fetal exposure to acetaminophen in cord blood (fetal blood).
31509360	Chen, 2019	Taiwan, nationwide	Births: 1998-2008	Exposure in any trimester: OR = 1.20; 95% CI, 1.01-1.42 Exposure in second trimester: OR = 1.19; 95% CI, 1.00-1.40 Exposure in first and second trimesters: OR = 1.28; 95% CI, 1.00 1.64	Nested Case-control study	950 study pairs (mothers-children-with-ADHD) and 3,800 control pairs (mothers-children-without-ADHD)	No missing data (national mandatory database)	Cases: diagnoses of ADHD by board-certified psychiatrists. Controls: randomly (1:4) identified and matchd by mothers ages, children s sex and ages, mothers age during pregnancy, income, and urbanization level	Prescriptions from the National Taiwan database;over the counter use and adherence to prescription was not captured.	ADHD from ICD-9 codes recorded in the Taiwan Health Insurance Database	**Variable selection:** a priori **Indication:** None **Other variables:** age, sex, income, level of urbanization, gestational infections, and comorbid perinatal conditions.	
30923825	Liew, 2019	Boston, MA	Births: 1993-2005	OR = 1.34, 95% CI: 1.05, 1.72	Prospective cohort	N=8,856	No details included in the paper	Participants in the Nurses Health Study II who were asked to fill up a medication use questionnaire on the same year they were pregnant	Maternal self report of regular acetaminophen use during the year of the child s birth	Maternal report of ADHD diagnosis in 2013	**Variable selection:** a priori **Indication:** None **Other variables:** maternal age at the child s birth, child s birth order, child s birth year, maternal gestational diabetes, preeclampsia, and self-reported regular maternal use of aspirin or other nonsteroidal antiinflammatory drugs, and ketoprofen. Sensitivity analyses included many other variables including maternal social factors, maternal smoking and alcohol drinking during each pregnancy,	
30458756	Tovo-Rodirgues, 201	Pelota, Brazil	Births: 2004	**ALL SUBJECTS:** OR=1.10 (95% CI, 0.87–1.39) at 6 years OR=1.20 (95%CI 0.96–1.49) at 11 years **BOYS:** OR = 1.42; (95%CI: 1.06–1.92) at 6 years OR = 1.31; 95% CI: 0.99–1.73 at 11 years	Prospective cohort	N=3470 (age 6 analysis); N=3447 (age 11 analysis)	No details included in the paper	All singleton live births in Pelota in 2044	Maternal self report of acetaminophen use at the post-delivery examination	Score ≥ 7 for inattention/hyperactivity symptoms on the Strengths and Difficulties Questionnaire (SDQ) - evaluated at age 6 and 11 years	**Variable selection:** a priori **Indication:** None **Other variables:** National Economic Index score (an SES estimator), sex, maternal educational level, age, skin color, parity, smoking during pregnancy, alcohol during pregnancy, mood issues during pregnancy, infections during pregnancy, prepregnancy BMI; and other nonsteroidal analgesic use during pregnancy.	The authors cautioned that the proportion of reported acetaminophen use during pregnancy was much lower than expected (27% vs. 51% expected based on other independent data in the region). Misreporting is likely to have diluted the effects, resulting in a weaker association

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
Not in Pubmed	Gustavson, 2021 (Overall Study)	Norway	Pregnancies: 1999 - 2008	**Adjusted HR (aHR) for long-term exposure (29 days or more)** = 2.02, 95% C.I = 1.17–3.25. **aHR for short-term exposure (1-7 days)** = 0.87, 95% C.I. = 0.70-1.08 **aHR for short-term exposure (8-28 days)** = 0.87, 95% C.I. = 0.70-1.08	Cohort	N=26,613	Exclusion	Pregnant women from all over Norway were invited to their routine ultrasound examination in gestational week 17.	Maternal questionnaires at gestational weeks 17 and 30.	Hyperkinetic disorder (F90) according to the 10th revision of the International Classification of Diseases (World Health Organization, 1993)	**Variable selection:** a priori **Indication:** pain conditions, fever/infections, chronic autoimmune or inflammatory conditions, unspecified conditions, and other conditio. **Other variables:** birth, parity, child's sex, maternal age, maternal educational level, smoking, alcohol use, and symptoms of depression and anxiety.	
Not in Pubmed	Gustavson, 2021 (Sibling controlled study; controlled for family effect)	Norway	Pregnancies: 1999 - 2008	**aHR in the sibling control model - long-term exposure (29 days or more) - adjusted by family effect** = 1.06 (95% C.I. = 0.51–2.05) at the within-family level	Cohort	Only discordant siblings contributed to power; siblings were discordant on exposure for 29 days and the outcome in **34** families; the total number of discordant siblings was	Exclusion	Pregnant women from all over Norway were invited to their routine ultrasound examination in gestational week 17.	Maternal questionnaires at gestational weeks 17 and 30.	Hyperkinetic disorder (F90) according to the 10th revision of the International Classification of Diseases (World Health Organization, 1993)	**Variable selection:** a priori **Indication:** pain conditions, fever/infections, chronic autoimmune or inflammatory conditions, unspecified conditions, and other conditio. **Other variables:** birth, parity, child's sex, maternal age, maternal educational level, smoking, alcohol use, and symptoms of depression and anxiety.	The analysis emphasized in the paper (>29 days of use) is based on a very small sample size. By design, the adjustment by family effect controls not only for confounders but also for intermediates; therefore, the results are largely uninformative
28031314	Liew, 2016	Denmark	Births: 1996-2002	OR = 1.5, 95% CI 1.0, 2.5 for subnormal overall attention OR = 1.5, 95% CI 1.0, 2.4 for selective attention difficulties OR = 1.5, 95% CI 0.9, 2.3 for parent-rated subnormal executive function. No significant associations with executive function.	Prospective cohort	N=1,491	inverse probability weights to account for refusals to participate	multiple imputations to address missing covariate values in all analyses (< 4% with at least one missing value).	Maternal self reportsat gestational weeks 12 and 30 and 6 months postpartum	At 5 yrs of age, trained psychologists assessed child s attention using the Test of Everyday Attention for Children at Five (TEACh-5). Parents and preschool teachers completed Behaviour Rating Inventory of Executive Function (BRIEF).	**Variable selection:** a priori **Indication:** fever, inflammation or infection, and pain or musculoskeletal diseases (adjusted for; also addressed in subgroup analysis restricted to women who did not reported the indications) **Other variables:** Maternal age at delivery, parity, IQ, mental health, pre-pregnancy BMI, smoking during pregnancy, alcohol intake during pregnancy, parental education, child s sex, neuropsychological tester, and prenatal use of aspirin and ibuprofen	Dose response relationships for the associations with global attention and metacognition index for executive function.
27353198	Avella-Garcia, 2016	Spain	Births 2004-2007	IRR=1.25, 95%CI: 0.93–1.69 for ADHD IRR = 1.41, 95% CI 1.01-1.98 for attention/impulsivity symptoms	Prospective cohort	N=1,382	NA	Residents in the cohort area, at least 16 years old, singleton pregnancy, planning to give birth at the reference hospital	Maternal self reports of acetaminophe use collected at weeks 12 and 32 of pregnancy.	In person evaluation using ADHD Criteria of the DSM-IV at a mean age of 4.8 years to identify hyperactivity/inattention symptoms	**Variable selection:** a priori + associations with outcome & exposure **Indication:** fever, UTI, maternal chronic illnesses (included in the models and stratified for) **Other variables:** cohort, child gender, age at testing, gestational age at birth, and maternal social class, education, IQ.	Children were evaluated for ADHD when they were 4.8 years of age in average.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
27533796	Stergiakouli , 2016	Avon, UK	Births: 1991-1992	RR=1.27; 95% CI, 1.05-1.53 (18 wk assessment) RR=1.43, 95% CI 1.18-1.73 (32 wk assessment)	Prospective cohort	N=7,996	Addressed using inverse-probability-weighting (<1% missing)	Pregnant women living in Avon, United Kingdom, with expected delivery dates from April 1991 to December 1992	Maternal self-reports of acetaminophen use in the previous three months collected at 18 and 32 weeks of pregnancy.	Strength and Difficulties Questionnaire (SDQ) at age 7 years	**Variable selection:** a priori **Indication:** muscle and joint problems, infections (cold or flu, urinary, or other infections), migraine, headaches.. **Other variables:** maternal age at birth, parity, socioeconomic status, smoking and alcohol during pregnancy, prepregnancy BMI, self-reported psychiatric illness, postnatal use, and partner's use	Postnal maternal acetaminophen use and partner's use were not associated with ADHD. These were used as negative control exposures to exclude unmeasured/unknown confounders. Polygenic Risk Scores for ADHD were not associated with acetaminophen use, indicating that confounding by genetic factors was unlikely in this population. N.B. This study is based on the ALSPAC cohort in Avon, UK. Leppert , 2019 also reported data on the same cohort in a paper investigating the association between genetics and ADHD risk factors, which included also a secondary analysis on acetaminophen and ADHD. Because Stergiakouli 2016 is the paper from ALSPAC specifically focusing on prenatal acetaminophen and ADHD, this paper is reported here while Leppert was not considered.
25251831	Thompson, 2014	Auckland, Australia	Births: 1995-1997	β=1.1 (0.2, 2.0) for parent SDQ at 7 yrs β=0.8 (-0.1, 1.8) for parent SDQ at 11 yrs β=1.1 (0.2, 2.0) for child SDQ at 11 yrs	Prospective cohort	N=871	NA	Only children born to mothers of European Ancestry were included	Maternal self-reports of acetaminophen use collected soon after delivery	Strength and Difficulties Questionnaire (SDQ) and Conner's Parent Rating Scale-Revised at age 7 and 11 years	**Variable selection:** a priori **Indication:** High fever **Other variables:** Small for gestational age, sex, age, paternal smoking during pregnancy, maternal education, smoking, during pregnancy, marital status at birth, parity, socioeconomic status, pre-pregnancy BMI, stress in the last month of pregnancy, alcohol in the first trimester, living with the child s biological father at 3.5 and child activity levels at 3.5, visiting health care provider for psychological conditions including depression and anxiety, taking medication during pregnancy for psychological conditions.	Results from using Parent Conner's test are similar though moderately less significant. The SDQ results are included because they feature assessments based both on parents and child's ratings.
24566677	Liew, 2014	Norway, nationwide	Pregnancies: 1996-2002	**RRs for total SDQ>16:** RR=1.13 (1.01-1.27) (any acetaminophen use) RR=1.24 (1.03-1.48) (use in all 3 trimesters) **HRs for hospital-diagnosed hyperkinetic disorder:** RR=1.37 (1.19-1.59) (any acetaminophen use) RR=1.61 (1.30-2.01) (use in all 3 trimesters) **ADHD medication:** HR=1.29 (1.15-1.44) (any acetaminophen use) HR=1.44 (1.21-1.72) (use in all 3 trimesters)	Prospective cohort	N=64,322	multiple imputation	Pregnant women from approximately 50% of all general practitionersin Denmark; women who spoke insuffiecient Danish or did not intend to complete their pregnancy were excluded	Maternal self-reports during pregnancy collected via three telephone interviews.	Parent's Standardized Strengths and Difficulties Questionnaire (SDQ) at age 7 years; hospital diagnosis of hyperkinetic disorders (ICD10: F90.0-F90.9); use of ADHD medications in the Danish Prescription Registry	**Variable selection:** a priori **Indication:** muscle and joint diseases, fever, and inflammation or infections. **Other variables:** child s birth year, birth weight, and sex; maternal age at child s birth, parity, gestational age at delivery, socioeconomic status, smoking and alcohol during pregnancy, prepregnancy BMI, self-reported psychiatric illnesses.	Acetaminophen use was collected using a telephone-based computer-assisted interview that asked about a list of 44 common pain killers.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
3603404	Streissguth, 1987	Seattle, WA	Pregnancies: 1974-75	beta=-3.25, SE=6.92; p=0.64 for the association between acetaminophen use in the first half of pregnancy and the attention score used in the study	Prospective cohort	N=355	Exclusion	Consecutive group of women seeking prenatal care	Maternal self-reports at the 5th month of pregnancy	Attention tested with a vigilance paradigm (Streissguth, 1984)	**Variable selection:** a priori **Indication:** None **Other variables:** Aspirin, antibiotics, alcohol, caffeine, and nicotine use during pregnancy, nutrition during pregnancy, maternal education, age, and birth order, as well as for the interaction between alcohol and nicotine	The attention score used in the study presents challenges in comparing it with the standardized methods used today.

PMID	Author	1. Selection: Was the strategy for recruiting participants consistent across study groups?	2. Blinding: Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?	3. Exposure: Were exposure assessment methods lacking accuracy?	4. Outcomes: Were outcome assessment methods lacking accuracy?	5. Confounding: Was potential confounding inadequately incorporated?	6. Were incomplete outcome data inadequately addressed?	7. Does the study report appear to have selective outcome reporting?	8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?	9. Did the study appear to have other problems that could put it at a risk of bias?	AVERAGE	Notes
34046850	Alemany, 2021	1	1	2	1	2	1	1	1	1	**1.2**	This study included five cohort.
31664451	Ji, 2020	1	1	1	1	1	1	1	1	1	**1.0**	Major strenghts in addressing bias due to objective masures of exposure in cord blood
31042271	Leppert, 2019	1	1	2	1	4	1	1	1	4	**1.8**	The analysis was only adjusted for age at ASD assessment and sex; the study was conducted to investigate the genetics of ASD and only marginally focused on acetaminophen
27353198	Avella-Garcia, 2016	1	1	2	1	1	1	1	1	1	**1.1**	
31565625	Saunders, 2019	4	4	4	2	4	1	1	1	4	**2.8**	Retrospective study with minimal consideration of epidemiological methods, including confounding, prospective design, control selection, and (9)adjustment for matching variables.
26688372	Liew, 2016	1	1	2	1	1	1	1	1	1	**1.1**	

Source: The Navigation Guide to Assess Risk of Bias in Toxicology and Environmental Health Studies
https://guides.himmelfarb.gwu.edu/systematic_review/reporting-quality-risk-of-bias

1 Low Risk of Bias
2 Probably Low Risk of Bias
3 Probably High Risk of Bias
4 High Risk of Bias
NA Not applicable

PMID	Author, Year	A. Size	b. Large Effect (>2)	c. Dose Response	d. Internal consistency	e. control of bias	f. Other	Sum of criteria	Strenght of Evidence (Initial score)	Expert opinion score on study quality	Notes
34046850	Alemany, 2021	2	0	0	2	1	NA	5	**1**	**1**	
31664451	Ji, 2020	0	2	2	2	2	2	10	**2**	**2**	d. Measurements in cord blood; f. stratification by fever
27353198	Avella-Garcia, 2016	1	0	0	2	1	NA	4	**1**	**1**	
26688372	Liew, 2016	2	1	2	2	1	NA	8	**2**	**2**	
Low quality studies (Excluded from the final evaluation of the strength of evidence)							0	0			
31042271	Leppert, 2019	2	0	0	-2	-2	NA	-2	**0**	**-2**	Opinion based score lower because age and sex are the only variables adjusted for. This study indeed focused on the association between polygenic risk scores and ASD. The analysis of ASD and acetaminophen was just supporting information included in supplementary materials
31565625	Saunders, 2019	-1	0	0	-2	-2	NA	-5	**-1**	**-2**	Opinion score driven by retrospective design with minimal consideration of epidemiological methods, including confounding, prospective design, control selection, and adjustment for matching variables.

Table - Grading of Strength of Each Study

Score	**Study of Evidence**
+2	**Very Strong**
+1	**Strong**
0	**Moderate**
-1	**Weak**
-2	**Very weak/none**

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
34046850	Alemany, 2021	United Kingdom, the Netherlands, Denmark, Italy, Spain, and Greece	Pregnancies: 1991-2008	OR = 1.19, 95% CI 1.07–1.3	Prospective cohorts	N=73,881	NA	Mother-Children with available data on either prenatal or postnatal exposure to acetaminophen and at least one outcome (ADHD or ASD)	Mothers were interviewed 2-4 times during pregnancy using standardized questionnaires. Regarding postnatal acetaminophen exposure, mothers were interviewed or completed questionnaires about medication use in their children 1-2 times in the first 18 months of life of the child.	Subscale of the CBCL11⁄2-5 and CBCL6/18 and the ADHD Criteria of DSM-IV (DSM-ADHD Questionnaire)	**Variable selection:** a priori **Indication:** None. **Other variables:** Maternal and child covariates: age at delivery (years), education (low, medium, high), pre-pregnancy body-mass index (BMI), alcohol (yes/no), smoking (yes/no) and men- tal health problems (yes/no) during pregnancy, age at birth (years) and parity (nulliparous, > 1 and > 2), maternal fever (yes/no) and infections (yes/no) during pregnancy; sex, age at behavioural assessment (years), cold (yes/no) and respira- tory infections (yes/no) in the first 2 years of life.	The exposure was assessed using maternal questionnaires or interviews. N.B.: This paper presents a combined analysis of 6 cohort studies in Europe. Two of them had reported results in other previous publications (Avella Garcia, 2016; Leppert 2019). However, these two cohorts amounted to just approximately 10% of the entire sample size of this new combined study, which was therefore considered as including predominantly new original data.
31664451	Ji, 2020	Boston, MA	Births: 1998-	Reference: Lowest tertile 2nd tertile: OR 2.14 (95% CI, 0.93-5.13) 3rd tertile: OR 3.62 (95% CI, 1.62-8.60)	Prospective cohort	N=996	Missing data for sociodemographic characteristics (<4%) imputed using multiple imputation by chained equations (MICE) with the Predictive Mean Matching method	Mothers who delivered singleton live births at Boston Medical Center (BMC), excluding conception via in vitro fertilization, deliveries induced by maternal trauma, or newborns with major birth defects.	Measurement of acetaminophen in cord blood samples (Fetal blood)	Diagnosis from Electronic medical records through 9.8 years of age in average	**Variable selection:** a priori, variables associated with exposure and outcome. **Indication:** stratified analyses by fever showed no differences between strata **Other variables:** maternal and child variables: maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal BMI, parity, child's sex, delivery type, preterm birth, and low birth weight.	Objective measurements of fetal exposure to acetaminophen in cord blood (fetal blood).
31042271	Leppert, 2019	Avon, UK	Births: 1991-1992	RR=0.76; 95% CI, 0.51-1.13	Prospective cohort	N=7,786	Addressed using inverse-probability-weighting (<1% missing)	Pregnant women living in Avon, United Kingdom, with expected delivery dates from April 1991 to December 1992	Maternal self report for the first and second half of pregnancy. Info was collected at visits during pregnancy and delivery.	a) being diagnosed with Pervasive Developmental Disorder using questions from the DAWBA questionnaire at 91 months or b) mother's self report	**Variable selection:** a priori **Indication:** None **Other variables:** sex and age at ASD assessment.	This study was designed to test the influence of maternal polygenic risk scores for neurodevelopmental disorders associated with early-life exposures, including acetaminophen exposure. N.B. This study is based on the ALSPAC cohort in Avon, UK. Stergiakouli , 2016 conduted a study dedicated specifically to prenatal acetaminophen and ADHD. THerfore, Stergiakouli , 2016 is presented in the ADHD tables, while Leppter 20190 is omitted in those tables.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
27353198	Avella-Garcia, 2016	Spain	Births 2004-2007	CAST scores were increased in ever-exposed males (b ¼ 0.63, 0 09–1.18). Increased effect sizes of risks by frequency of use were observed for hyperactivity/impulsivity symptoms (IRR ¼ 2.01, 0 95–4.24) in all children, K-CPT commission errors (IRR ¼ 1.32, 1.05–1.66) and detectability (b ¼[1]0.18, [1]0.36–0.00) in females, and CAST scores in males (b ¼ 1 91, 0.44–3.38).	Prospective cohort	N=1,255	NA	Women residing in the cohort area, at least 16 years old, singleton pregnancy, planning to give birth at the reference hospital	Maternal self reports of acetaminophe use collected at weeks 12 and 32 of pregnancy.	In person evaluation using Childhood Autism Spectrum Test (CAST)13 which quantifies autism spectrum symptoms in children (each point represents one symptom of ASC with a cut-off of 15 or more points, having a 100% sensitivity and 97% specificity for ASC	**Variable selection:** a priori + associations with outcome & exposure **Indication:** fever, UTI, maternal chronic illnesses (included in the models and stratified for) **Other variables:** cohort, child gender, age at testing, gestational age at birth, and maternal social class, education, IQ.	Children were evaluated for ASD when they were 4.8 years of age in average.
31565625	Saunders, 2019	Saint John, Canada	Not specified, Ethics Board approval in 2013-2014	Not provided, but not significant (p=0.66)	Case-control	N=215 (107 ASD cases and 108 controls)	14 participants with missing data were excluded	ASD cases identifed from clinical records, four local pediatricians, and recruitment posters; controls from recruitment posters, matched by sex and age.	Maternal self reports at the time of the study (after ASD diagnoses), when children were between 0-10 years of age.	ASD diagnoses before age 6 years, reported by the mother.	None considered	In addition to no consideration of confounders, matching variables were not considered
26688372	Liew, 2016	Denmark	Births: 1996-2002	HR=1.19 (95% CI 1.04-1 35) HR = 1 51, 95% CI 1.19, 1 92 for ASD with hyperkinetic symptoms. HR = 1 06, 95% CI 0 92, 1 24 for other types of ASD	Prospective cohort	N=64,322	Multiple imputation for missing values in covariates (<5% of participants)	pregnancies between 1996-2002, recruited at weeks 6-12. Exclusion criteria: women who did not speak Danis or did not intend to carry their pregnancy to ter.	Maternal self reportsat gestational weeks 12 and 30 and 6 months postpartum	ASD hosptial admissions from the Danish National Hospital Registry Danish Psychiatric Central Registry	**Variable selection:** a priori **Indication:** fmaternal fever, inflammation/infection, or diseases in muscle/joint **Other variables:** child's sex, birth year, maternal age, parity, socioeconomic status, maternal smoking and alcohol drinking during pregnancy, and maternal prepregnancy BMI, self-reported maternal psychiatric illness, nonsteroidal anti-inflammatory drugs, maternal folic acid supplementary intake.ter, and prenatal use of aspirin and ibuprofen	Dose response relationship for duration of use

PMID	Author	1. Selection: Was the strategy for recruiting participants consistent across study groups?	2. Blinding: Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?	3. Exposure: Were exposure assessment methods lacking accuracy?	4. Outcomes: Were outcome assessment methods lacking accuracy?	5. Confounding: Was potential confounding inadequately incorporated?	6. Were incomplete outcome data inadequately addressed?	7. Does the study report appear to have selective outcome reporting?	8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?	9. Did the study appear to have other problems that could put it at a risk of bias?	AVERAGE	Notes
33230558	Inoue, 2021	1	1	2	1	1	1	1	1	1	**1.1**	
31448449	Tronnes, 2020	1	1	2	1	1	2	1	1	1	**1.2**	
31965601	Bertoldi, 2020	1	1	2	1	1	1	1	1	1	**1.1**	
31693212	Parker, 2020	3	2	3	2	1	2	1	1	1	**1.8**	Not a population-based study, but a case-control study for craniofacial malformation.
31637744	Rifas-Shiman, 2020	1	1	2	1	1	1	1	1	1	**1.1**	
32196712	Tovo-Rodriguez, 2020	1	1	3	1	1	1	1	1	1	**1.2**	Collection of data about acetaminophen exposure is very wide (perinatal period) and did not include dose.
30202886	Laue, 2019	1	1	1	1	1	1	1	1	2	**1.1**	Limited sample size
31523834	Golding, 2019	1	1	2	1	2	2	1	1	2	**1.4**	
29331486	Bornehag, 2018	1	1	1	1	2	2	1	1	2	**1.3**	Adjustment was not adequate, and did not include confounding by indication. There is no information about how they handled missing data.
29550610	Ruisch, 2018	1	1	2	1	2	2	1	1	2	**1.4**	
28168770	Skovlund, 2017	1	1	1	3	1	1	1	1	1	**1.2**	The language grammar rating scale is not a widely accepted method.
27479646	Liew, 2016	1	1	2	1	1	1	1	1	1	**1.1**	
27585674	Vlenterie, 2016	1	1	2	1	1	2	1	1	1	**1.2**	
24163279	Brandlistuen, 2013	1	1	2	1	1	1	1	1	1	**1.1**	
3603404	Streissguth, 1987	1	1	2	1	1	2	1	1	1	**1.2**	

Source: The Navigation Guide to Assess Risk of Bias in Toxicology and Environmental Health Studies
https://guides.himmelfarb.gwu.edu/systematic_review/reporting-quality-risk-of-bias

1 Low Risk of Bias
2 Probably Low Risk of Bias
3 Probably High Risk of Bias
4 High Risk of Bias
NA Not applicable

PMID	Author, Year	A. Size	b. Large Effect (>2)	c. Dose Response	d. Internal consistency	e. Control of bias	f. Other	Average of criteria	Sum of criteria	Strenght of Evidence	Expert opinion score on study quality	Notes
33230558	Inoue, 2021	2	0	1	2	1		1.2	6	1	1	
31448449	Tronnes, 2020	2	1	0	0	1		0.8	4	1	1	
31965601	Bertoldi, 2020	1	0	0	2	0		0.6	3	1	1	This is two studies in one. Not really a thing
31693212	Parker, 2020	0	0	0	2	1		0.6	3	1	0	Not a population-based study, but a case-control study for craniofacial malformation.
31637744	Rifas-Shiman, 2020	1	1	2	2	1		1.4	7	1	1	
32196712	Tovo-Rodriguez, 2020	1	-1	0	2	1		0.6	3	1	0	Lack of accuracy in the assessment of the exposure was noted (questionnaires during the perinatal period). No dose was included.
31523834	Golding, 2019	2	0	0	2	0		0.8	4	1	0	The list of confounders is limited. Authors recognize potential residual confounding.
30202886	Laue, 2019	-2	-1	0	0	2		-0.2	-1	0	-1	Limited sample size
29331486	Bornehag, 2018	**0**	**2**	**0**	**0**	**-1**		**0.2**	**1**	**0**	**0**	In general, it is a well-designed study. Adjustment is a concern, but exposure assessment is a strength.
29550610	Ruisch, 2018	2	1	0	2	-1		0.8	4	1	1	
28168770	Skovlund, 2017	2	0	2	2	0		1.2	6	1	1	
27479646	Liew, 2016	**1**	**1**	**0**	**1**	**1**		**0.8**	**4**	**1**	**1**	
27585674	Vlenterie, 2016	2	0	0	2	1		**1.0**	5	1	1	
24163279	Brandlistuen, 2013	**1**	**1**	**0**	**2**	**1**		**1.0**	**5**	**1**	**1**	
3603404	Streissguth, 1987	-1	-1	0	0	1		**-0.2**	-1	0	0	This study has a limited sample size.

Table - Grading of Strength of Each Study

Score	**Study of Evidence**
+2	**Very Strong**
+1	**Strong**
0	**Moderate**
-1	**Weak**
-2	**Very weak/none**

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
33230558	Inoue, 2021	Denmark	1996–2002	**Risk Ratios (RR) for Behavioral Difficulties at Age 11 Years According to Prenatal Exposure to Acetaminophen:** Parent reported: Strengths and Difficulties Questionnaire (SDQ) - composite score: 1.14 (95% CI: 1.01, 1.29). Internalizing: 1.09, (95% CI: 1.00, 1.19). SDQ - Emotional symptoms: 1.16 (95% CI: 1.09 -1.24). Hyperactivity: 1.12 (1.02, 1.24). Child-reported: Strengths and Difficulties Questionnaire (SDQ) - composite score: 1.40 (95% CI: 1.20, 1.63). Internalizing: 1.13, (95% CI: 1.04, 1.23). Externalizing: 1.13, (95% CI: 1.05, 1.22). SDQ - Emotional symptoms: 1.17 (95% CI: 1.02 -1.34). Hyperactivity: 1.18 (1.08, 1.29).	Cohort	N = 40,934	Multiple imputation (Ten simulated complete data sets were generated assuming multivariate normal distribution for about 8% of participants who had at least 1 missing covariate value)	Mothers, with live-born children, whose answered the study enrollment form and the 3 subsequent telephone interviews (12th and 30th gestational weeks and at 6 months after birth).	Information about acetaminophen exposure was obtained from the study enrollment form and 3 computer-assisted telephone interviews.	Children s behaviors were assessed based on the standardized Strengths and Difficulties Questionnaire (SDQ).	Potential confounders were selected a priori, including mother s age at childbirth, parity, socio-occupational status, maternal prepregnancy body mass index, and birth year. They additionally adjusted for maternal smoking during pregnancy, maternal alcohol intake during pregnancy, mother s self-reported psychiatric illnesses before and during pregnancy, indications for maternal acetaminophen use (including diseases of muscles or joints during pregnancy, episodes of fever during pregnancy, and inflammation/infections during pregnancy), and prenatal use of nonsteroidal antiinflammatory drugs such as aspirin and ibuprofen.	This study showed very consistent associations.
31448449	Tronnes, 2020	Norway	1999 - 2008	**Paracetamol exposure during pregnancy and behavioural problems in preschool-age**: Paracetamol use in three trimesters: Adjusted RR: 1.36 (1.02, 1.80). **Paracetamol exposure during pregnancy and temperamental traits**: Paracetamol use in two trimesters - Shyness: Adjusted RR: -0.62 (95% CI −1.05, −0.19)	Cohort	N = 32,934	NA (not even in the supplementary material)	Pregnant women at their routine ultrasound examination at gestational week 17–18	Information about medication use was obtained from two prenatal questionnaires.	Communication skills were assessed by the Ages and Stages Questionnaire (ASQ). Selected items from The Child Behaviour Checklist (CBCL) for preschool children (CBCL/ 1.5–5) were used to assess children s behaviour. Temperament was assessed by the short version of the Emotionality, Activity and Shyness Temperament Questionnaire (EAS). All outcomes were parent-reported when the child was 5 years old.	Confounders selected a priori: maternal age at delivery, marital status, education level, parity, pre-pregnancy body mass index (BMI), folic acid supplement, smoking habits, alcohol use, symptoms of anxiety and depression (measured by a short version of the Hopkins Symptoms Checklist (SCL-5)30), maternal health conditions during pregnancy, concomitant medication use, and child sex.	Pain conditions, headache or migraine, and fever or infection were questioned.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
31965601	Bertoldi, 2020	USA - Brazil	1999 and 2002, Project Viva; Pelotas 2015	**Project Viva:** Exposure to acetaminophen in both the 1st and 2nd trimester of pregnancy and early childhood cognitive outcomes: Wide Range Achievement of Visual Motor Abilities (WRAVMA) - drawing: β: -1.53 (95% CI: -2.93, -0.13) Exposure to acetaminophen during pregnancy: WRAVMA - drawing: β: -0.63 (95% CI: -1.20, -0.06) **Pelotas cohort**: Exposure to acetaminophen in both the 1st and 2nd trimester of pregnancy and early childhood cognitive outcomes: INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA): Total: β: 0.09 (95% CI: 0.02, 0.16). Exposure to acetaminophen during the 1st 2nd and 3rd trim: INTER-NDA: Total: β: 0.10 (95% CI: 0.02, 0.18)	Cohorts	Project Viva: N = 1,217. Pelotas: N = 3,818	To address the issue of missing outcome data, they implemented inverse probability weighting (IPW). They did not use multiple imputation because most covariates had <5% missing values.	Project Viva: Women with single pregnancies, who had intention to remain in the geographical area, were fluent in English and presented by the 22nd week of gestation. Pelotas: All women who gave birth in any of the five maternity hospitals of the city of Pelotas from 1 January to 31 December 2015, and lived in the urban area of the municipality, were invited to participate.	Project Viva: Mothers were asked to categorize their acetaminophen use during this pregnancy for the early pregnancy interview (1st trimester) and in the past 3 months for the mid-pregnancy interview (2nd trimester). Pelotas: Women were asked about any medication use during pregnancy at prenatal and perinatal interviews.	Project Viva: Children's cognition using the Peabody Picture Vocabulary Test (PPVT-III) and the Wide Range Achievement of Visual Motor Abilities (WRAVMA). Pelotas: Children's cognitive development at a 24-month follow-up visit was evaluated using the INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA).	Project Viva: Maternal reported age at enrollment, race/ethnicity, education, household income, parity, alcohol intake during pregnancy, smoking status, ibuprofen use during pregnancy, and pre-pregnancy body mass index, antibiotic use, depressive symptoms, child sex and birth- weight, child's day care attendance, respiratory tract infections since birth, and use of ibuprofen ≥6 times in the first year of life. Pelotas: age, education level, self-reported skin colour, and family income, parity, any smoking and alcohol intake during pregnancy, prenatal depressive/ anxiety symptoms, any antibiotic use during pregnancy, and ibuprofen use during pregnancy, pre-pregnancy BMI, and newborn sex at birth.	This is two studies in one
31693212	Parker, 2020	USA and Canada	1996 - 2002	Any use of acetaminophen was associated with mother-reported behavioral problems (mean differences [MD] 2.2, 95% CI 0.3, 4.1). The MD was similar for both internalizing (MD 2.5, 95% CI 0.8, 4.3) and externalizing (MD 1.9, 95% CI 0.1, 3.7) broadband scales	Cohort	N= 560	NA	Data on maternal exposures during pregnancy and at least one neurodevelopmental assessment in childhood.	Standardized interview administered after delivery and prior to childhood neurodevelopmental assessments.	The Child Behavior Checklist (CBCL) and the Teacher-Report Form (TRF), tests that are part of the Achenbach System of Empirically Based Assessment (ASEBA), were used to assess common child behavior problems.	Covariates in the adjusted models were selected a priori and included maternal age, race, education, marital status, parity, drinking and smoking during early pregnancy. Models were also adjusted for four indication categories: headache, fever, pain, and upper respiratory infection without fever, including allergy.	Data used in this analysis were originally collected as part of a study of risk factors for and sequelae of a craniofacial malformation, hemifacial microsomia. Controls were non-malformed children that were matched to cases on birth year and pediatric practice or practices within the same zip code. Memory bias may be affecting the results (nterviews after delivery).

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
31637744	Rifas-Shiman, 2020	USA	1999 - 2002	Acetaminophen during pregnancy (≥10 versus <10 times) and mid- childhood executive function and behavoiur. Behaviour Rating Inventory of Executive Function (BRIEF) Global Executive Composite: β 1 64 (95% CI 0.59, 2.68). Behaviour Regulation Index: β 1.45 (95% CI 0.44, 2.47). BRIEF Metacognition Index: β 1 29 (95% CI 0.29, 2.30). Infancy exposure (≥6 versus <6 times) to acetaminophen and higher parent-rated BRIEF - Global Executive Composite score (GEC) scores: BRIEF - Global Executive Composite: β 1.69 (95% CI 0 51, 2.87). Behaviour Regulation Index: β 1.26 (95% CI 0.08, 2.45). BRIEF Metacognition Index: β 1 67 (95% CI 0.54, 2.81). Strengths and Difficulties Questionnaire (SDQ) Total Difficulties: β 1.19 (95% CI 0 58, 1.80).	Cohort	N = 1,225	Multiple imputation	Women with single pregnancies, who had intention to remain in the geographical area, were fluent in English and presented by the 22nd week of gestation	Mothers were asked to categorize their acetaminophen use during this pregnancy for the early pregnancy interview (1st trimester) and in the past 3 months for the mid-pregnancy interview (2nd trimester)	Behavoiur Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ)	Age, education, parity, pregnancy smoking status, and household income and their child s race/ethnicity, depressive symptoms in mid-pregnancy using the Edinburgh Postpartum Depression Scale (EPDS), antidepressant and antibiotic use during pregnancy, infant sex, birthweight.	The consistency of results in this study is impressive.
32196712	Tovo-Rodriguez, 2020	Brazil	2004	**Acetaminophen during pregnancy and neurodevelopmental performance**: Low performance in BDI: RR 1.00 (0.78, 1.28) Social-personal area: RR 1.00 (0.80, 1.25). Adaptative area: RR 0.91 (0.76, 1.08). Motor area RR 0.91 (0.71, 1.16). Communication area: RR 1.04 (0.84, 1.30). Cognitive area: RR 0.92 (0.83, 1.02).	Cohort	N = 3,737	Missing data was handled using inverse probability weighting (IPW).	Mothers were those living in the urban area of Pelotas or in Jardim América.	Standardised questionnaire applied at the perinatal evaluation. The use of acetaminophen was defined as at least once during pregnancy, regardless of the dose used.	The screening version of Battelle's Developmental Inventory (BDI) was used to assess the children's development at 24 months of age. Child behavioural/ emotional problems were assessed at 48 months using the Child Behaviour Checklist (CBCL)	Family Wealth Index Quotient (WIQ) in the month prior to delivery, maternal schooling, age, skin colour, marital status, parity, smoking during pregnancy, alcohol consumption during pregnancy, mood symptoms during pregnancy, pre-gestational body mass index, prenatal care (number of antenatal care appointments attended during pregnancy), infectious diseases during pregnancy, high blood pressure and diabetes mellitus diagnosis during pregnancy, usage of other nonsteroidal analgesic, and child sex.	Collection of data about acetaminophen exposure is very wide (perinatal period) and did not include dose.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
31523834	Golding, 2019	UK	1991 - 1992	Mean differences in cognition and behaviour measures and paracetamol exposure at 18-32 wk gestation: IQ - Freedom from distractibility at 8y: Adjusted mean difference (AMD): -0.35 (95% CI -0.69, -0.00). M.SDQ Hyperactivity at 42 mo: AMD +0.16 (95% CI +0.07, +0.25). M.SDQ Hyperactivity at 47 mo: AMD: +0.22 (95% CI +0.10, +0.33). Development and Well-being Assessment (T.DAWBA) Attention at 7-8 y: AMD: +0.45 (95% CI +0.11, +0.79). T.DAWBA Attention/ Activity at 7-8 y: AMD: +0.53 (95% CI +0.02, +1.04).	Cohort	N = 12,418	NA	Pregnant women who were resident in Avon, UK with at least one questionnaire had been returned, and no misscarriage.	Questionnaire at about 32 weeks gestation.	Strengths and Difficulties Questionnaire (SDQ). 18 measures of cognitive function considered, the eleven relating to IQ (not clear what test they used). 11 measures of the child's temperament (not clear	The identification of potential confounders used an exposome technique that involves the identifying all factors that were associated at P < .0001 with paracetamol intake at 32 weeks gestation in unadjusted analyses. This included Medical history (history of asthma, history of indigestion, history of back pain, history of migraine, pre-pregnancy BMI), comorbidity in the period 18-32 (ppor health, cold, other infections, headach), healthy diet score, processed diet score, alcohol consumption, domestic social score, Parity +1.	Early during-pregnancy exposure may be missed (memory bias). Also, this study only included exposure from 18-32 weeks, not earlier or later.
30202886	Laue, 2019	Canada	2007 - 2009	**Estimates for the association between prepregnancy acetaminophen exposure and neurocognitive development:** Coding: Low exposure: 1.03 (95% CI -0.22, 2.29). High exposure: 0.74 (-0.54, 2.01) Block Design subtest: Low exposure: 1.03 (95% CI -0.22, 2.29). High exposure: -0.92 (95% CI -2.20, 0.37)	Cohort	N = 118	Excluded	Pregnant women living in Sherbrooke, Quebec, Canada recruited between 2007 and 2009 during the first trimester of pregnancy and at delivery.	Acetaminophen was extracted from < 120 mg meconium by a solid-liquid extraction in ethyl acetate followed by a purification with a dispersive solid phase extraction in acetonitrile.	Neurocognitive development was evaluated using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)	Maternal characteristics (maternal age at delivery, maternal prepregnancy body mass index, parity, and maternal Raven Matrix score at the follow-up visit as a measure of maternal intelligence); child characteristics (sex, gestational age, birth weight, 5-min Apgar score, and age at follow up visit), and socioeconomic characteristics (maternal education and family income).	Sample size is very limited (N=118)
29550610	Ruisch, 2018	UK	1991 - 1992	Paracetamol exposure during pregnancy and oppositional-defiant disorder (ODD) and conduct disorder (CD) symptoms: ODD scores - Teacher rated: Incidence rate ratio (IRR): 1.21 (1.06, 1.38). CD symptom scores - Maternal rated: IRR 1.14 (1.05, 1.24). CD symtom scores - Teacher rated: 1.25 (1.01, 1.53)	Cohort	N ≈ 6,300 for maternal and N ≈ 4,400 for teacher ratings	NA	Pregnant women who were resident in Avon, UK with at least one questionnaire had been returned, and no misscarriage.	Questionnaires at 18 weeks gestation	Development and Well-Being Assessment (DAWBA).	Offspring sex, socioeconomic status, young maternal age (age < 20 at delivery), and single parent status during pregnancy. It also added genetic risk scores to the models.	Some relevant confounders were not included (infections, pain).
29331486	Bornehag, 2018	Switzerland	2007 - 2010	**Odds ratio (OR) for language delays among girls whose mothers reported >6 vs. 0 acetaminophen tablets during pregnancy:** 5.92 (95% confidence interval (CI) 1.10–31.94). **OR for LD in girls whose mothers' urinary APAP was in the highest compared to the lowest quartile**: 10.34 (95% CI 1.37–77.86).	Cohort	N = 754	NA	Pregnant women who could read Swedish and were not planning to move out of the country	Two exposure measures were used: (1) maternally reported number of acetamoniphen tablets taken between conception and enrollment; (2) acetaminophen urinary concentration at enrollment.	A nurse evaluation and a parental questionnaire on language use at 30 months of age.	Maternal weight, mother s education, smoking and week of enrollment. Urinary acetaminophen was creatinine-adjusted in all analyses	The adjustment is poor (e.g., no adjustment by indication), but the exposure assessement is a strength.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
28168770	Skovlund, 2017	Norway	1999 - 2008	**Odds ratios of having a child with lower communication skills according to use of paracetamol:** Two periods (trimesters): Adjusted OR 1.09 (95% CI 1.04–1.15) Three periods (trimesters): Adjusted OR 1.17 (95% CI 1.06–1.30)	Cohort	N = 58,410	Excluded	Pregnant women in Norway who accepted to participate prior to the first ultrasound scan at weeks 17–18.	Mothers were asked to report on medication use at pregnancy weeks 17–18 and 30.	Language competence at 3 years of age was evaluated by a validated language grammar rating scale (Dale, 2003; PMID: 14696985).	Maternal and paternal education level, marital status and maternal work situation during pregnancy, information on whether the pregnancy was planned or not, the use of folic acid supplements in early pregnancy, pre-pregnancy body mass index, maternal and paternal age and parity.	It was primarily designed to study opiods during pregnancy. The dose response is very suggestive.
27479646	Liew, 2016	Denmark	1996–2002	**Prenatal acetaminophen and IQ:** Mean difference in full-scale IQ in 1–5 weeks of use: -3.1 (95% CI: -5.6,-0.68). Mean difference in performance IQ in 1–5 weeks of use: -4.1 (95% CI: -7.3, -0.88)	Cohort	N = 1,491	Multiple imputation	The sampling was based on maternal alcohol and binge drinking reported during pregnancy with an oversampling strategy (high alcohol intake during pregnancy) to select the high-alcohol-exposed subgroup. Women who spoke insufficient Danish or did not intend to complete their pregnancy were excluded.	information about acetaminophen use was collected in three telephone interviews conducted at gestational weeks 12th and 30th.	Child iQ was assessed using the Wechsler Primary and Preschool Scales of intelligence-revised (WPPSi-r). The cohort used a shorter version that includes three verbal and three performance sub-tests designed to shorten test duration.	Confounders selected a priori: child s sex, mother s age at child birth, parity, parental education index, maternal iQ, maternal smoking during pregnancy, maternal average alcohol intake during pregnancy, and prenatal use of nonsteroidal anti-inflammatory drugs, such as aspirin and ibuprofen.	The oversampling was based on high alcohol consumption and only 51% participated of those invited. However, they used appropriate statistical analysis to correct for that.
27585674	Vlenterie, 2016	Norway	1999 - 2008	**Paracetamol exposure and psychomotor and behavioural outcomes in 18-omnth-old infants:** Psychomotor problems: Fine motor: OR: 1.17 (95% CI. 1.01-1.36) Delayed motor milestone attainment: OR: 1.35 (95% CI 1.07–1.70) Communication: OR: 1.32 (95% CI: 1.05-1.66) Behavioural problems: Externalizing: OR. 1.50 (95% CI 1.26-1.76)	Cohort	N = 51,200	NA	Pregnant women at their routine ultrasound examination at gestational week 17–18	Information about medication use was obtained from two prenatal questionnaires.	Psychomotor development at the age of 18 months was assessed by the Ages and Stages Questionnaire (ASQ). The Child Behaviour Checklist (CBCL/11/2-5/LDS) was used to assess behaviour at 18 months. Temperament among infants at the age of 18 months was assessed with the short-form Emotionality, Activity and Shyness Temperament Questionnaire (EAS).	Maternal age at delivery, pre-pregnancy body mass index, parity, marital status or cohabiting, maternal education, smoking and alcohol consumption and folic acid use. Maternal depressive symptoms were also included infections (genital, urinary, and respiratory), fever, headache or migraine, pelvic girdle pain, back pain, neck pain, abdominal pain and other pain were included. Medications (NSAIDs, antiepileptics, antidepressants, opioids, triptans and benzodiazepines) were also included.	Sensitivity analyses for several indications showed similar effects, suggesting no confounding by indication.

PMID	Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing data	Inclusion Criteria	Exposure Definition	Outcome definition	Confounders	Notes
24163279	Brandlistuen, 2013	Norway	1999 - 2008	**Prenatal paracetamol for more than 28 days**: Poorer gross motor development: β: 0.24, 95% CI 0.12–0.51 Poor communication: β: 0.20, 95% CI 0.01–0.39 Poor externalizing behaviour: β: 0.28, 95% CI 0.15–0.42 Poor internalizing behaviour: β: 0.14, 95% CI 0.01– 0.28 Higher activity levels: β: 0.24, 95% CI 0.11–0.38. **Short- term use of paracetamol (1–27 days)**: Poor gross motor outcomes: β: 0.10, 95% CI 0.02– 0.19	A sibling-controlled cohort study	N = 2,919 same-sex sibling pairs	Multiple imputation	NA	Information on paracetamol use was obtained from two prenatal questionnaires. Groups were divided in short-term (1-28 days of use) and long-term (28 days or more).	Psychomotor development was assessed by items from the validated Norwegian version of the Ages and Stages Questionnaire (ASQ). a Externalizing and internalizing behaviours were measured by the Child Behaviour Checklist (CBCL/ 11/2-5/LDS). S. Temperament was assessed by the Emotionality, Activity and Shyness Temperament Questionnaire (EAS).	Maternal: before and during pregnancy infections (respiratory, urinary tract/bladder, genital, diarrhoea/gastric flu), fever, back pain and headache or migraine. Concomitant use of nonsteroidal anti-inflammatory drugs, triptans, opioids, other analgesics, benzodiazepines, antidepressants, antipsychotics, and antiepileptic drugs (grouped as co-medication). Psychological distress (anxiety and depression) was also included. Other potential confounding factors included maternal age at delivery, years between pregnancies, parity, smoking during pregnancy and alcohol use during pregnancy.	
3603404	Streissguth, 1987	Seattle, USA	1974-1975	**IQ scores on aspirin and acetaminophen**: Linear model: Beta (SE): 0.28 (0.54), p-value: 0.61. Binary model: Beta (SE): 0.37 (0.54), p-value: 0.49.	Cohort	N = 421	NA	A consecutive group of pregnant women receiving prenatal care in 1974-1975, interviewed during the fifth month of pregnancy in their own homes.	Self-report at 5 months gestation.	Child IQ was assessed with the Weschler Preschool and Pri- mary Scale of Intelligence (WPPSD)	Maternal education, alcohol, nicotine, and caffeine consumption, antibiotic usage, mother's age, nuetritional status during pregnancy, maternal and paternal education, race, birth order, child's sex, socioeconomic status.	Lack of association could be linked with a limited sample size.

ANDREA BACCARELLI

MD, PhD

HIGHLIGHTS

Elected to the National Academy of Science for pioneering new approaches to identify and characterize chemical risks

Led global research and education in 40+ countries in Asia, Africa, Europe, South, Central, and North America

Impacted domestic and global policies and regulations

Recognized on the Web-of-Science list of the most influential investigators worldwide

President of the International Society of Environmental Epidemiology

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CURRENT POSITION

Columbia University Mailman School of Public Health, New York
Chair and Leon Hess Professor, Dept. of Environmental Health Sciences
2016 – Date

PREVIOUS POSITIONS

Harvard University, T.H. Chan School of Public Health, Boston, MA -
Associate Professor of Epidemiology and Environmental Health Sciences
2010-2016

Universita degli Studi di Milano, Milan, Italy
Assistant Professor of Environmental Health and Toxicology
2004-2010

Resident and Clinical Fellow, Internal Medicine and Endocrinology
1995-2000

PROFESSIONAL SERVICE

Elected Member, National Academy of Medicine, 2020 – date

President, International Society Environmental Epidemiology, 2021-date

Chair, Committee for the Use of Emerging Science for Environmental Health Decisions, National Academy of Sciences, 2022-date

Member, Environmental Protection Agency Review Panel – Environmental Chemical Dose Responses, 2014

EDUCATION

MD *summa cum laude*
1995 – University of Perugia, Italy

MPH in Epidemiology *summa cum laude*
2000 – University of Turin, Italy

PhD in Toxicology and Occupational Health *summa cum laude*
2003 – University of Milan, Italy

Post-doctoral training in Environmental Health and Toxicology
2005 – National Institutes of Health, Bethesda, MD

Detailed Professional Service and Honors

PROFESSIONAL SERVICE

2017- Date	Center Director, NIEHS P30 Center for Environmental Health and Justice in Northern Manhattan, Columbia University
2022 - Date	President, International Society for Environmental Epidemiology
2022 – Date	Co-chair, Committee on Emerging Science for Environmental Health Decisions, National Academy of Science, Medicine, and Engineering
2017 - Date	Director, Skills for Health and Research Professional (SHARP) Program for Professional Education in Precision Medicine and Public Health, Columbia University
2021-Date	Director, Career MODE (Careers through Mentoring and training in Omics and Data for Early-stage Investigators) R25 training program
2019 - 2021	Chair, Membership Committee, International Society for Environmental Epidemiology
2016-2018	Director, Interdisciplinary T32 Training in Environmental Health (T32ES007322), Columbia University Mailman School of Public Health
2019	Chair, External Review Committee, Gillings School of Global Public Health, Department of Environmental Sciences and Engineering, University of North Carolina at Chapel Hill
2018-2019	External Advisor, Target II Consortium, National Institute of Environmental Health Sciences
2019	Chair, Biostatistics Chair Search Committee, Columbia University, Mailman School of Public Health
2018	Co-Chair, Interdisciplinary Research Task Force, Columbia University, Mailman School of Public Health
2014-2016	Co-Director, Interdisciplinary T32 Training Program in Genes and the Environment (T32ES016645), Harvard T.H. Chan School of Public Health
2013- 2014	Member, Committee to Review EPA's Draft State-of-the-Science on Nonmonotonic Dose-Response Relationships as they Apply to Endocrine Disrupters, The National Academy of Science
2013	Committee Chair, Administration and Faculty Support Strategic Planning Committee, Department of Environmental Health, Harvard Chan School
2012-2018	Steering Group Member, International Genetics of DNA methylation Consortium (GoDMC)
2012-2018	Advisory Board Member, HELIX Molecular and Biochemical Exposome International European Project, International FP7 European Union Project
2011	Committee Member, External Review Committee of the Public Health Studies Program, Johns Hopkins University, Baltimore, MD
2010-2014	Leadership Committee Member, Council on Functional Genomics & Translational Biology, American Heart Association
2006-2010	Member, Educational Committee, Biotechnology Graduate Program, University of Milan

HONORS

2020-date	Included in the annua list of Highly Cited, World's Most Influential Researchers, Web of Science
2020	President Elect, International Society for Environmental Epidemiologists (ISEE)
2020-date	Elected Member, National Academy of Medicine
2019	Included in the 2019 List of Highly Cited, World's Most Influential Researchers of the Past Decade, Web of Science
2018	Person of the Year – Baiocco D'oro Award, City of Perugia, Italy
2017	Paper of the Year 2017, American Journal of Epidemiology and Society for Epidemiologic Research

2013	Classic Paper of the Year 2013, Environmental Health Perspectives
2012	Reviewer of the Year, Environmental Health Perspectives
2010	Fellow of the American Heart Association
2010	Drago Rivera Award for Environmental Sciences and Public Health Protection, Lombardia Academy of Sciences and Humanities, Milan, Italy
2008	Ricercatissimi Award for International Research Excellence, Lombardy Region Government, Milan, Italy
2005	International Research Collaboration Award - Italian Ministry of University and Scientific Research
2003	Research Excellence Award, PhD Program in Environmental Health, University of Milan, Italy
1995	Outstanding Medical Dissertation Award, School of Medicine, University of Perugia, Italy

Review and Editor Activities

GRANT REVIEW – NATIONAL INSTITUTES OF HEALTH

2021	Committee Member, NIH ENQUIRE, Center for Scientific Review (CSR)/NIH Evaluating Panel Quality in Review population science study sections
2020	Reviewer, Special Emphasis Panel, NIH Conflict Review panel for the Behavioral Genetics and Epidemiology (BGES) and Neurological, Aging and Musculoskeletal Epidemiology (NAME) study sections.
2020	Ad-Hoc Reviewer, NIH Loan Repayment Program, NIH/NIEHS
2015-2019	Chartered Member, NIH Kidney, Nutrition, Obesity & Diabetes (KNOD) Study Section
2014	Reviewer, Special Emphasis Panel ZES1 LWJ-J (K1), Pathway to Independence in Environmental Health Sciences (Teleconference)
2013	Reviewer, NIH Special Emphasis Panel ZRG1 DKUS 90S, Systemic Injury by Environmental Exposure (SIEE)
2013	Reviewer, NIH Special Emphasis Panel ZES1 LWJ-D (T2), Training and Career Grant Applications
2012	Reviewer, NIEHS Children's Center Review Meeting (P01)
2012	Ad-hoc scientific reviewer, NIH Mechanisms of Emotion, Stress and Health Study Section (MESH) Study Section
2012	Reviewer, NIH Special Emphasis Panel ZRG1 PSE-K, Neurological, Aging, and Musculoskeletal Epidemiology
2012	Reviewer, NIH Special Emphasis Panel ZES1 JAB-D(V), Virtual Consortium for Translational/Transdisciplinary Environmental Research
2012	Reviewer, NIH Special Emphasis Panel ZRG1 BBBP-J, RFA HL-12-037: Mechanistic Pathways Linking Psychosocial Stress and Behavior
2011	Ad-hoc scientific reviewer, NIH Biobehavioral Mechanisms of Emotion, Stress and Health (MESH) Study Section
2011	Reviewer, NIH Special Emphasis Panel ZRG1 PSE-K (Epidemiology)

GRANT REVIEW – OTHER FUNDING AGENCIES

- Agence Nationale de la Recherche, Paris, France
- American Heart Association, Genomics, Translational Biology and Observational Epidemiology (GTOE-1) Peer Review Committee.
- Belgian Cystic Fibrosis Association
- Belgian National Fund for Scientific Research
- European Union, 7th Framework Program
- Foundation Against Cancer, Brussels, Belgium
- Health Effects Institute, Boston, MA
- Italian Scientific Institutes for Health and Research (IRCCS)
- Mac Arthur Foundation
- Netherlands Asthma Foundation
- Qatar National Research Funds
- UK Wellcome Trust

EDITORIAL BOARD MEMBERSHIPS

2015-Date	Founding Editorial Board Member, Environmental Epigenetics
2012-Date	Editorial Advisory Board Member, Journal of Applied Toxicology
2013-2018	Associate Editor, Environmental Health Perspectives

Teaching and Invited Lectures

TEACHING

2021- Date	Environmental Determinants of Public Health II, Graduate Program, Columbia University – Mailman School of Public Health, New York, NY
2017-Date	Epigenetics Boot camp, Skills for Health and Research Professionals (SHARP) Program, Columbia University/Mailman School Precision Medicine Initiative, New York, NY
2017-2020	Public Health Epigenetics, Graduate Program, Columbia University – Mailman School of Public Health, New York, NY
2008-2016	Environmental Epigenetics, Exposure Epidemiology and Risk Graduate Program, Harvard Chan School, Boston, MA
2006-2010	Molecular Applications in Epidemiology, PhD Program in Occupational and Environmental Health, University of Milan, Italy
2004-2010	Applied Biotechnology, Graduate School of Biotechnology, University of Milan, Italy
2004-2006	Molecular Epidemiology, Graduate School of Biotechnology, University of Milan, Italy

GUEST LECTURES IN ACADEMIC COURSES

2019- Date	Environment, Health, and Justice: Concepts and Practice (PUBHW4200), Columbia University's Undergraduate Program
2017- Date	Molecular Epidemiology (P8307), Environmental Health Sciences Graduate Program, Columbia University – Mailman School of Public Health
2017- Date	Lifecourse Epidemiology (P8493), Epidemiology Graduate Program, Columbia University - Mailman School of Public Health
2013-2016	Genetic Epidemiology of Diabetes Obesity and Complex Diseases (EPI222), Harvard T.H. Chan School of Public Health
2012-2016	Interdisciplinary Training in Pulmonary Sciences (EH513), Harvard T.H. Chan School of Public Health
2012-2016	Environmental and Occupational Epidemiology (ID215), Harvard T.H. Chan School of Public Health
2012-2016	Biological Science Seminars (DBS205), Harvard T.H. Chan School of Public Health
2011-2016	Human Development Course (IN731.0), Harvard Medical School

Research funding

CURRENT FUNDING

P30ES009089 (Baccarelli) 04/01/2023 – 03/31/2028
NIH/NIEHS
Center for Environmental Health in Northern Manhattan
The NIEHS Center for Environmental Health in Northern Manhattan (CEHNM) brings together scientists, physicians, epidemiologists, biostatisticians and citizens in a partnership focusing on a central theme that stresses understanding and preventing the environmental components of disease.
Role on Project: Center Director

R01ES032818 (Baccarelli, Herbstman, Mason) 04/01/2021 –03/31/2026
NIH/NIEHS
Prenatal Traffic-Related Air Pollutants, Placental Epitranscriptomics, and Child Cognition
The project aims to uncover the impacts of traffic-related air pollutants on neurodevelopment in a low-income population of African American and Latinx children. The goal of the project is to elucidate the role of the placental epitranscriptome and the ensuing effects on child neurodevelopment.
Role: PI

UG3/UH3OD023337 (RJ Wright/RO Wright) 09/21/2016 – 08/31/2023
NIH/OD
ECHO Consortium on Perinatal Programming of Neurodevelopment
This project links highly experienced environmental health scientists with statisticians, social epidemiologists, stress researchers, child psychologists, chemists, pediatricians, toxicologists, geneticists, and epigeneticists to build the infrastructure and scientific capacity to create a highly functional, state-of-the-art longitudinal birth cohort consortium that objectively measures human environments that program child health and integrates with the greater NIH ECHO program.
Role: Sub-contract PI

R35ES031688 (Baccarelli) 07/05/2021 – 6/30/2029
NIH/ NIEHS
Extracellular vesicles in Environmental Epidemiology Studies of Aging
The purpose of this project is to identify early biological responses to environmental exposures that are predictive of future health-related conditions, specially of the effects of air pollution on accelerated brain aging.
Role: PI

R25GM143298 (Baccarelli, Ionita, Miller) 08/15/2021-07/31/2026
NIH / NIGMS
The 'Career MODE' Program: Careers through Mentoring and training in Omics and Data for Early-stage investigators
The purpose of this proposal is to train a new generation of diverse biomedical investigators and provide them with skills, knowledge, mentoring, professional skills, and networking to foster their pathways to independence using omics and data science.
Role: Multiple Principal Investigator

R01AG069120 (Baccarelli, Yaffe, Hou) 07/15/2020 –04/30/2025
NIH/NIA
Blood mitochondrial DNA biomarkers of midlife cognitive decline and adverse brain imaging changes - A longitudinal investigation in the CARDIA population-based cohort study
This study characterizes novel blood-based biomarkers to identify preclinical ADRD and test their utility in predicting clinical ADRD. The cohorts will let us determine the clinical utility of these mtDNA biomarkers to predict clinical ADRD and move the field closer of personalized health interventions.
Role: Multiple Principal Investigator

R01ES032638 (Navas-Acien, Baccarelli, Mason) 01/01/2021-10/31/2025
NIH/NIEHS
The Epitranscriptome as a Novel Mechanism of Arsenic-Induced Diabetes.

The objective of this study is to evaluate novel epitranscriptomic mechanisms for arsenic-related diabetes in participants from the Strong Heart Study.
Role: Multiple Principal Investigator

R01ES032242 (Colicino, Baccarelli) 09/01/2020-06/30/2025
NIH/NIEHS
Air Particulate Pollution and Stress: Effects and Mechanisms for Long-term Maternal Obesity Risks
The purpose of this project is to identify novel biomarkers that is associated with air pollution exposure and psychosocial stress to maternal postpartum obesity. The project utilizes the PROGRESS cohort based in Mexico and biospecimens are shipped to New York for analyses.
Role: Multiple Principal Investigator

K99/R00ES030749 (Kupsco) 5/11/2020 – 4/30/2025
Mentor
NIH/NIEHS
Prenatal Exposures to Flame-Retardants: Mitochondrial Signatures and Childhood Obesity
This Career Development Award aims to characterize the effects of prenatal exposures to polybrominated diphenyl ether (PBDE) flame retardants on childhood adiposity, examining mitochondrial DNA content and mutations as potential mechanistic biomarkers. The project utilizes the Children's Center of Environmental Health cohort based in New York for analysis. This award also aims to position Dr. Kupsco as an independent investigator in mitochondriomics and children's environmental health.
Role: Mentor

RF1AG071024 (Casey) 04/01/2021 – 03/31/2024 .
NIH/NIA
Short and long-term consequences of wildfires for Alzheimer's disease and related dementias
Increasing threat from wildfire exposures necessitates studies of their effect on the aging US population. The proposed research uses millions of patient records from the Medicare cohort and electronic health record data from a large healthcare system to advance NIA and NIEHS goals to understand the role of joint environmental and social exposures in age-related disease. This work will provide critical information on important subgroups to target for early intervention and lead to recommendations to reduce the negative impact of wildfire-related PM2.5 or disaster exposure on MCI or AD/ADRD and to prevent, delay, or slow progression of dementia to promote the well-being of older adults.
Role: Co-investigator

R01AG074359 (Casey) 01/09/2021 – 05/31/2026
NIH/NIA
Historical social and environmental determinants of memory decline and dementia among U.S. older adults.
Increasing threat from wildfire exposures necessitates studies of their effect on the aging US population. The proposed research uses millions of patient records from the Medicare cohort and electronic health record data from a large healthcare system to advance NIA and NIEHS goals to understand the role of joint environmental and social exposures in age-related disease. This work will provide critical information on important subgroups to target for early intervention and lead to recommendations to reduce the negative impact of wildfire-related PM2.5 or disaster exposure on MCI or AD/ADRD and to prevent, delay, or slow progression of dementia to promote the well-being of older adults.
Role: Co-investigator

Publications

PUBLICATION METRICS

- 618 total publications.
- H-index: 111 (Google Scholar)
- Total citations: 47,300 (Google Scholar)

FULL LIST OF ARTICLES IN PEER-REVIEWED JOURNALS

Live List of Published Work in PubMed

1. Wu H, Eckhardt CM, Baccarelli AA. Molecular mechanisms of environmental exposures and human disease. *Nat Rev Genet.* 2023.
2. Baccarelli A, Dolinoy DC and Walker CL. A precision environmental health approach to prevention of human disease. *Nature Communications.* 2023;14(1):2449.
3. Herrera-Moreno JF, Prada D, Baccarelli AA. Early Environment and Telomeres: a Long-Term Toxic Relationship. *Curr Environ Health Rep.* 2023.
4. Campisi M, Mastrangelo G, Mielzynska-Svach D, Hoxha M, Bollati V, Baccarelli AA, Carta A, Porru S, Pavanello S. The effect of high polycyclic aromatic hydrocarbon exposure on biological aging indicators. *Environ Health.* 2023;22(1):27.
5. Jiang Y, Huang J, Li G, Wang W, Wang K, Wang J, Wei C, Li Y, Deng F, Baccarelli AA, Guo X, Wu S. Ozone pollution and hospital admissions for cardiovascular events. *Eur Heart J.* 2023.
6. Sumner JA, Gao X, Gambazza S, Dye CK, Colich NL, Baccarelli AA, Uddin M, McLaughlin KA. Stressful life events and accelerated biological aging over time in youths. *Psychoneuroendocrinology.* 2023;151:106058.
7. Prada D, Crandall CJ, Kupsco A, Kioumourtzoglou MA, Stewart JD, Liao D, Yanosky JD, Ramirez A, Wactawski-Wende J, Shen Y, Miller G, Ionita-Laza I, Whitsel EA, Baccarelli AA. Air pollution and decreased bone mineral density among Women's Health Initiative participants. *EClinicalMedicine.* 2023;57:101864.
8. Dye CK, Domingo-Relloso A, Kupsco A, Tinkelman NE, Spratlen MJ, Bozack AK, Tellez-Plaza M, Goessler W, Haack K, Umans JG, Baccarelli AA, Cole SA, Navas-Acien A. Maternal DNA methylation signatures of arsenic exposure is associated with adult offspring insulin resistance in the Strong Heart Study. *Environ Int.* 2023;173:107774.
9. Kupsco A, Bloomquist TR, Hu H, Reddam A, Tang D, Goldsmith J, Rundle AG, Baccarelli AA, Herbstman JB. Mitochondrial DNA copy number dynamics and associations with the prenatal environment from birth through adolescence in a population of Dominican and African American children. *Mitochondrion.* 2023;69:140-146.
10. Lv Y, Yang Z, Ye L, Jiang M, Zhou J, Guo Y, Qiu Y, Li X, Chen C, Ju A, Wang J, Li C, Li Y, Wang J, Zhang J, Ji JS, Li T, Baccarelli AA, Gao X, Shi X. Long-term fine particular exposure and incidence of frailty in older adults: findings from the Chinese Longitudinal Healthy Longevity Survey. *Age Ageing.* 2023;52(2).
11. Reddam A, Bollati V, Wu H, Favero C, Tarantini L, Hoxha M, Comfort N, Gold DR, Phipatanakul W, Baccarelli AA. Air Pollution and Human Endogenous Retrovirus Methylation in the School Inner-City Asthma Intervention Study. *Toxicol Sci.* 2023.
12. Hardy F, Takser L, Gillet V, Baccarelli AA, Bellenger JP. Characterization of childhood exposure to environmental contaminants using stool in a semi-urban middle-class cohort from eastern Canada. *Environ Res.* 2023;222:115367.
13. Do WL, Sun D, Meeks K, Dugue PA, Demerath E, Guan W, Li S, Chen W, Milne R, Adeyemo A, Agyemang C, Nassir R, Manson JE, Shadyab AH, Hou L, Horvath S, Assimes TL, Bhatti P, Jordahl KM, Baccarelli AA, Smith AK, Staimez LR, Stein AD, Whitsel EA, Narayan KMV, Conneely KN. Epigenome-wide meta-analysis of BMI in nine cohorts: Examining the utility of epigenetically predicted BMI. *Am J Hum Genet.* 2023;110(2):273-283.
14. Danesh Yazdi M, Nassan FL, Kosheleva A, Wang C, Xu Z, Di Q, Requia WJ, Comfort NT, Wu H, Laurent LC, DeHoff P, Vokonas P, Baccarelli AA, Schwartz JD. Short-term air pollution and temperature exposure and changes in the extracellular microRNA profile of Normative Aging Study (NAS) participants. *Environ Int.* 2023;171:107735.

15. Machtinger R, Racowsky C, Baccarelli AA, Bollati V, Orvieto R, Hauser R, Barnett-Itzhaki Z. Recombinant human chorionic gonadotropin and gonadotropin-releasing hormone agonist differently affect the profile of extracellular vesicle microRNAs in human follicular fluid. *J Assist Reprod Genet.* 2023;40(3):527-536.
16. Parsons E, Rifas-Shiman SL, Bozack AK, Baccarelli AA, DeMeo DL, Hivert MF, Godderis L, Duca RC, Oken E, Cardenas A. Prenatal trimester-specific intake of micronutrients: global DNA methylation and hydroxymethylation at birth and persistence in childhood. *J Dev Orig Health Dis.* 2023;14(2):311-318.
17. Baker BH, Joo YY, Park J, Cha J, Baccarelli AA, Posner J. Maternal age at birth and child attention-deficit hyperactivity disorder: causal association or familial confounding? *J Child Psychol Psychiatry.* 2023;64(2):299-310.
18. Wang C, Xu Z, Qiu X, Wei Y, Peralta AA, Yazdi MD, Jin T, Li W, Just A, Heiss J, Hou L, Zheng Y, Coull BA, Kosheleva A, Sparrow D, Amarasiriwardena C, Wright RO, Baccarelli AA, Schwartz JD. Epigenome-wide DNA methylation in leukocytes and toenail metals: The normative aging study. *Environ Res.* 2023;217:114797.
19. Burris HH, Gerson KD, Woodward A, Redhunt AM, Ledyard R, Brennan K, Baccarelli AA, Hecht JL, Collier AY, Hacker MR. Cervical microRNA expression and spontaneous preterm birth. *Am J Obstet Gynecol MFM.* 2023;5(1):100783.
20. Wang C, DeMeo DL, Kim ES, Cardenas A, Fong KC, Lee LO, Spiro A, 3rd, Whitsel EA, Horvath S, Hou L, Baccarelli AA, Li Y, Stewart JD, Manson JE, Grodstein F, Kubzansky LD, Schwartz JD. Epigenome-Wide Analysis of DNA Methylation and Optimism in Women and Men. *Psychosom Med.* 2023;85(1):89-97.
21. Qureshi F, Aris IM, Rifas-Shiman SL, Perng W, Oken E, Rich-Edwards J, Cardenas A, Baccarelli AA, Enlow MB, Belfort MB, Tiemeier H. Associations of cord blood leukocyte telomere length with adiposity growth from infancy to adolescence. *Pediatr Obes.* 2023;18(1):e12977.
22. Eckhardt CM, Gambazza S, Bloomquist TR, De Hoff P, Vuppala A, Vokonas PS, Litonjua AA, Sparrow D, Parvez F, Laurent LC, Schwartz J, Baccarelli AA, Wu H. Extracellular Vesicle-Encapsulated microRNAs as Novel Biomarkers of Lung Health. *Am J Respir Crit Care Med.* 2023;207(1):50-59.
23. Gagnon A, Grenier G, Bocti C, Gillet V, Lepage JF, Baccarelli AA, Posner J, Descoteaux M, Takser L. White matter microstructural variability linked to differential attentional skills and impulsive behavior in a pediatric population. *Cereb Cortex.* 2023;33(5):1895-1912.
24. Lieberman-Cribbin W, Domingo-Relloso A, Navas-Acien A, Cole S, Haack K, Umans J, Tellez-Plaza M, Colicino E, Baccarelli AA, Gao X, Kupsco A. Epigenetic Biomarkers of Lead Exposure and Cardiovascular Disease: Prospective Evidence in the Strong Heart Study. *J Am Heart Assoc.* 2022;11(23):e026934.
25. Munoz-Manrique C, Trejo-Valdivia B, Hernandez-Cordero S, Cantoral A, Deierlein AL, Colicino E, Niedzwiecki MM, Wright RO, Baccarelli AA, Tellez-Rojo MM. Weight gain trajectories patterns from pregnancy to early postpartum: identifying women at risk and timing to prevent weight regain. *BMC Pregnancy Childbirth.* 2022;22(1):811.
26. Campana AM, Laue HE, Shen Y, Shrubsole MJ, Baccarelli AA. Assessing the role of the gut microbiome at the interface between environmental chemical exposures and human health: Current knowledge and challenges. *Environ Pollut.* 2022;315:120380.
27. Gao X, Huang J, Cardenas A, Zhao Y, Sun Y, Wang J, Xue L, Baccarelli AA, Guo X, Zhang L, Wu S. Short-Term Exposure of PM(2.5) and Epigenetic Aging: A Quasi-Experimental Study. *Environ Sci Technol.* 2022;56(20):14690-14700.
28. Jain P, Binder A, Chen B, Parada H, Gallo LC, Alcaraz J, Horvath S, Bhatti P, Whitsel EA, Jordahl K, Baccarelli AA, Hou L, Stewart JD, Li Y, LaMonte MJ, Manson JE, LaCroix AZ. The association of epigenetic age acceleration and multimorbidity at age 90 in the Women's Health Initiative. *J Gerontol A Biol Sci Med Sci.* 2022.
29. Uddin MDM, Nguyen NQH, Yu B, Brody JA, Pampana A, Nakao T, Fornage M, Bressler J, Sotoodehnia N, Weinstock JS, Honigberg MC, Nachun D, Bhattacharya R, Griffin GK, Chander V, Gibbs RA, Rotter JI, Liu C, Baccarelli AA, Chasman DI, Whitsel EA, Kiel DP, Murabito JM, Boerwinkle E, Ebert BL, Jaiswal S, Floyd JS, Bick AG, Ballantyne CM, Psaty BM, Natarajan P, Conneely KN. Clonal hematopoiesis of indeterminate potential, DNA methylation, and risk for coronary artery disease. *Nat Commun.* 2022;13(1):5350.
30. Kupsco A, Sjodin A, Cowell W, Jones R, Oberfield S, Wang S, Hoepner LA, Gallagher D, Baccarelli AA, Goldsmith J, Rundle AG, Herbstman JB. Prenatal exposure to polybrominated diphenyl ethers and BMI Z-scores from 5 to 14 years. *Environ Health.* 2022;21(1):82.
31. Comfort N, Wu H, De Hoff P, Vuppala A, Vokonas PS, Spiro A, Weisskopf M, Coull BA, Laurent LC, Baccarelli AA, Schwartz J. Extracellular microRNA and cognitive function in a prospective cohort

of older men: The Veterans Affairs Normative Aging Study. *Aging (Albany NY)*. 2022;14(17):6859-6886.
32. Oluwayiose OA, Wu H, Gao F, Baccarelli AA, Sofer T, Pilsner JR. Aclust2.0: a revamped unsupervised R tool for Infinium methylation beadchips data analyses. *Bioinformatics.* 2022;38(20):4820-4822.
33. Liu Z, Shen J, Barfield R, Schwartz J, Baccarelli AA, Lin X. Large-Scale Hypothesis Testing for Causal Mediation Effects with Applications in Genome-wide Epigenetic Studies. *J Am Stat Assoc.* 2022;117(537):67-81.
34. Jiang M, Wang X, Gao X, Cardenas A, Baccarelli AA, Guo X, Huang J, Wu S. Corrigendum to "Association of DNA methylation in circulating CD4(+) T cells with short-term PM(2.5) pollution waves: A quasi-experimental study of healthy young adults" [Ecotoxicol. Environ. Saf. 239 (2022) 1-8/113634]. *Ecotoxicol Environ Saf.* 2022;243:113970.
35. Laue HE, Shen Y, Bloomquist TR, Wu H, Brennan KJM, Cassoulet R, Wilkie E, Gillet V, Desautels AS, Abdelouahab N, Bellenger JP, Burris HH, Coull BA, Weisskopf MG, Zhang W, Takser L, Baccarelli AA. In Utero Exposure to Caffeine and Acetaminophen, the Gut Microbiome, and Neurodevelopmental Outcomes: A Prospective Birth Cohort Study. *Int J Environ Res Public Health.* 2022;19(15).
36. Jain P, Binder AM, Chen B, Parada H, Jr., Gallo LC, Alcaraz J, Horvath S, Bhatti P, Whitsel EA, Jordahl K, Baccarelli AA, Hou L, Stewart JD, Li Y, Justice JN, LaCroix AZ. Analysis of Epigenetic Age Acceleration and Healthy Longevity Among Older US Women. *JAMA Netw Open.* 2022;5(7):e2223285.
37. Lee AG, Tignor N, Cowell W, Colicino E, Bozack A, Baccarelli A, Wang P, Wright RJ. Associations between antenatal maternal asthma status and placental DNA methylation. *Placenta.* 2022;126:184-195.
38. Eckhardt CM, Wu H, Prada D, Vokonas PS, Sparrow D, Hou L, Schwartz J, Baccarelli AA. Predicting risk of lung function impairment and all-cause mortality using a DNA methylation-based classifier of tobacco smoke exposure. *Respir Med.* 2022;200:106896.
39. Solomon O, Huen K, Yousefi P, Kupers LK, Gonzalez JR, Suderman M, Reese SE, Page CM, Gruzieva O, Rzehak P, Gao L, Bakulski KM, Novoloaca A, Allard C, Pappa I, Llambrich M, Vives M, Jima DD, Kvist T, Baccarelli A, White C, Rezwan FI, Sharp GC, Tindula G, Bergstrom A, Grote V, Dou JF, Isaevska E, Magnus MC, Corpeleijn E, Perron P, Jaddoe VWV, Nohr EA, Maitre L, Foraster M, Hoyo C, Haberg SE, Lahti J, DeMeo DL, Zhang H, Karmaus W, Kull I, Koletzko B, Feinberg JI, Gagliardi L, Bouchard L, Ramlau-Hansen CH, Tiemeier H, Santorelli G, Maguire RL, Czamara D, Litonjua AA, Langhendries JP, Plusquin M, Lepeule J, Binder EB, Verduci E, Dwyer T, Carracedo A, Ferre N, Eskenazi B, Kogevinas M, Nawrot TS, Munthe-Kaas MC, Herceg Z, Relton C, Melen E, Gruszfeld D, Breton C, Fallin MD, Ghantous A, Nystad W, Heude B, Snieder H, Hivert MF, Felix JF, Sorensen TIA, Bustamante M, Murphy SK, Raikkonen K, Oken E, Holloway JW, Arshad SH, London SJ, Holland N. Meta-analysis of epigenome-wide association studies in newborns and children show widespread sex differences in blood DNA methylation. *Mutat Res Rev Mutat Res.* 2022;789:108415.
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43. Jiang M, Wang X, Gao X, Cardenas A, Baccarelli AA, Guo X, Huang J, Wu S. Association of DNA methylation in circulating CD4(+)T cells with short-term PM(2.5) pollution waves: A quasi-experimental study of healthy young adults. *Ecotoxicol Environ Saf.* 2022;239:113634.
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52. Gao F, Zhang W, Baccarelli AA, Shen Y. Predicting chemical ecotoxicity by learning latent space chemical representations. *Environ Int.* 2022;163:107224.
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Andrea Baccarelli, M.D., Ph.D, MPH
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Exhibit A

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186. Any materials included in my curriculum vitae and anything cited or included in my case-specific report if not listed here.

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190. Deposition of Carol Jeffcoat (5/25/2023) and attached exhibits.

191. Deposition of Edwin Kuffner (5/24/2023) and attached exhibits.

192. Deposition of Islah Ahmed (6/1/2023) and attached exhibits.

193. Deposition of Leslie Shur (5/26/2023) and attached exhibits.

194. Deposition of Rachel Weinstein (5/19/2023) and attached exhibits.

195. DSM-V Sections re: Neurodevelopmental Disorders, ASD, ADHD.

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